EMA/CHMP/289566/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ongentys	Opicapone
Ontilyv	Opicapone

Procedure No. EMEA/H/C/xxxx/WS/2552

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse Drug Reaction
BIAL	BIAL-Portela & Cª SA
BMI	Body Mass Index
CI	Confidence Interval
CGI-I	Clinical Global Impression of Improvement
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double-blind
DB-FAS	Double-blind Full Analysis Set
DB-PPAS	Double-blind Per Protocol Analysis Set
DB-SAF	Double-blind Safety Analysis Set
DDCI	Dopa Decarboxylase Inhibitor
ECG	Electrocardiogram
EMA	European Medicines Agency
ENT	Entacapone
EOS	End-of-study
EU	European Union
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
ISDB	Integrated Safety Database
L-DOPA	Levodopa
LS	Least Square
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MAO	Monoamine Oxidase
MAR	Missing-at-random
MCID	Minimal Clinically Important Difference

MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society Unified Parkinson’s Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mMIDI	Modified Minnesota Impulsive Disorder Interview
MMRM	Mixed Model for Repeated Measures
N/A	Not Available
NMSS	Non-motor Symptoms Scale
OL	Open-label
OPC	Opicapone
PDQ-39	Parkinson’s Disease Questionnaire
PDSS-2	Parkinson’s Disease Sleep Scale 2
PGI-I	Patient’s Global Impression of Improvement
PSV	Post-study Visit
PT	Preferred Term
QD	quaque die, Once Daily
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
vs.	Versus
UPDRS	Unified Parkinson’s Disease Rating Scale
WSA	Worksharing Applicant
WOQ-9	9-item Wearing-off Questionnaire

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bial - Portela & Cª, S.A. submitted to the European Medicines Agency on 25 July 2023 an application for a variation following a worksharing procedure (WS) according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of signs and symptoms of Parkinson's Disease for Ongentys/Ontilyv, based on final results from study BIA-91067-303. This is a pivotal Phase III, multicentre, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of opicapone (OPC) in patients with early idiopathic Parkinson's Disease receiving treatment with L-DOPA plus a DDCI, and who are without signs of any motor complication.

As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

Version 6.1 of the RMP has also been submitted (only applicable to Ongentys) to reflect the changes made upon approval of the informed consent application, to keep consistency between the eCTD lifecycles of the two marketing authorisations (Ongentys and Ontilyv) and to include the new proposed indication.

Furthermore, the PI is brought in line with the latest QRD template version 10.3. In addition, as part of the application the MAH is requesting a 1-year extension of the market protection.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

With reference to Article 7, 8 and 30 of Regulation (EC) No 1901/2006 ('paediatric regulation') this section is required as of 26 January 2009 for applications for new indications.

Pursuant to Article 13 of Regulation (EC) No. 1901/2006 as amended, BIAL-Portela & Ca S.A. submitted to the European Medicines Agency on 16 February 2023 an application for a product-specific waiver on the grounds set out in Article 11 of said Regulation for OPC.

The Paediatric Committee, having assessed the waiver application in accordance with Article 13 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended report:

To grant a product-specific waiver for all subsets of the paediatric population and for the treatment of Parkinson's disease in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Rapporteur's comment

A waiver (class waiver) to develop OPC in the paediatric population was granted by the European Medicines Agency (EMA) on 14 January 2011. On 26 May 2023, the Paediatric Committee issued a decision on the granting of a specific product waiver (EMEA-003406-PIP01-23). No clinical study was conducted in children since Parkinson's disease (non-juvenile) is subject to a Paediatric Investigational Plan product waiver (EMEA-003406-PIP01-23).

Information relating to orphan market exclusivity

N/A

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

WSA request for additional market protection

The WSA requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. See separate AR on one year additional market protection for new indication.

Scientific advice

Study 303 was designed to meet the criteria outlined by the Committee for Medicinal Products for Human Use (CHMP) guideline of clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP/330418/2012 rev. 2, 2012). Scientific advice (SA) concerning this extension of indication was sought from the EMA. BIAL requested scientific advice from the EMA on 15 May 2020, and advice was provided by the agency to BIAL on 23 July 2020 (EMEA/H/SA/2250/2/2020/II). The SA pertained to the following clinical aspects: Overall design, patient population, endpoints, statistical analysis plan and length of double-blind treatment period in the study. All of the advice topics provided have been addressed, as appropriate, including adaptation of study design. The scientific advice document given for these questions is provided by the MAH in Module 1.2.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of signs and symptoms of Parkinson's Disease for

Ongentys/Ontilyv, based on final results from study BIA-91067-303; this is a pivotal Phase III, multicentre, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of OPC in patients with early idiopathic Parkinson's Disease receiving treatment with L-DOPA plus a DDCI, and who are without signs of any motor complication. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.1 of the RMP has also been submitted (only applicable to Ongentys) to reflect the changes made upon approval of the informed consent application, to keep consistency between the eCTD lifecycles of the two marketing authorisations (Ongentys and Ontilyv) and to include the new proposed indication. Furthermore, the PI is brought in line with the latest QRD template version 10.3. In addition, as part of the application the MAH is requesting a 1-year extension of the market protection.

Grounds for refusal

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

3. Recommendations following re-examination

☐ is finally not approvable since a major objection and other concerns have been identified, which preclude a recommendation at the present time.

☐ is finally approvable <since other concerns <major objections> <has><have> all been resolved>.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'

5. Scientific discussion

5.1. Introduction

5.1.1. Problem statement

Disease or condition

Parkinson's disease (PD) is an idiopathic neurodegenerative disorder of the central nervous system that affects both the motor system and non-motor systems. The disease is characterised by the loss of dopamine-generating cells resulting in a significant decrease in cerebral dopamine levels which becomes symptomatic over a certain threshold. The symptoms usually emerge slowly, and as the disease worsens, non-motor symptoms become more common. Early symptoms are tremor, rigidity, slowness of movement, and difficulty with walking. Problems may also arise with cognition, behaviour, sleep, and sensory systems. PD dementia becomes common in advanced stages of the disease. The motor symptoms of the disease result from the death of nerve cells in the substantia nigra, a region of the midbrain that supplies dopamine to the basal ganglia. Collectively, the main motor symptoms are known as Parkinsonism or a Parkinsonian Syndrome[1].

State the claimed the therapeutic indication

This is a type II variation application to request an extension of use for Ongentys/Ontilyv 50 mg in the following indication: *"Adjunctive therapy to preparations of L-DOPA/DDCI in adult patients for the treatment of signs and symptoms of Parkinson's disease"*.

5.1.2. About the product

Opicapone (development code: BIA 9-1067) is a third generation, peripheral, selective, long-acting and reversible catechol O methyltransferase (COMT) inhibitor developed by BIAL-Portela & Ca SA (hereinafter referred to as BIAL) to be used in combination (adjunct treatment) with levodopa (L-DOPA) and a peripheral levodopa/dopa decarboxylase inhibitor (DDCI) in adult patients with Parkinson's Disease (PD) and end-of-dose motor fluctuations that cannot be stabilised on those combinations. In the presence of DDCI, COMT becomes the major metabolising enzyme for L-DOPA, catalysing its conversion to 3 O methyldopa in the brain and periphery. By decreasing the activity of COMT, opicapone (OPC) increases the bioavailability of L DOPA and provides a more continuous dopaminergic stimulation in patients with Parkinson's disease[2].

OPC has proven to be generally well-tolerated and efficacious in reducing OFF-time in patients with Parkinson's disease and end-of-dose motor fluctuations (Study BIA 91067 301 and Study BIA-91067-302 of the initial MAA). The long therapeutic action of OPC enables once-daily dosing that is not dictated by the timing of L-DOPA administration, thereby helping avoid the fluctuations in L-DOPA pharmacokinetics that are associated with the development and expression of motor fluctuations, and potentially providing a more continuous delivery of L-DOPA than that was possible with earlier COMT

[1] Kalia LV, Lang AE (August 2015). "Parkinson's disease". Lancet. 386 (9996): 896–912
[2] Almeida L, Rocha J, Falcão A, Nuno Palma P, Loureiro A, Pinto R, et al. Pharmacokinetics, Pharmacodynamics and Tolerability of Opicapone, a Novel Catechol-O-Methyltransferase Inhibitor, in Healthy Subjects. Clin Pharmacokinet. 2013 Feb 1;52(2):139–51.

inhibitors[3]. The rationale for the addition of once-daily OPC 50 mg to oral L-DOPA/DDCI therapy is to ultimately enhance the clinical benefit of oral L-DOPA in patients with Parkinson's disease with or without motor complications.

With this type II variation application the MAH requests an extension of use for *Ongentys*/*Ontilyv* 50 mg in the early stage of the disease for the following indication: "*Adjunctive therapy to preparations of L DOPA/DDCI in adult patients for the treatment of signs and symptoms of Parkinson's disease*".

5.1.3. The development programme/compliance with CHMP guidance/scientific advice

On 24 June 2016, the European Commission granted approval of *Ongentys* as an adjunctive therapy to preparations of L-DOPA/DDCI in adult patients with Parkinson's disease and end of-dose motor fluctuations who cannot be stabilised on those combinations (MA No. EU/1/15/1066/001-010). The OPC marketing authorisation application (MAA) was renewed in February 2021 with unlimited validity. OPC is also authorised by the European Commission since 21 February 2022 under the tradename *Ontilyv* relating to informed consent from *Ongentys*. OPC is currently authorised for marketing under the latter indication in 44 countries, including the EU countries, the United Kingdom, Switzerland, the United States of America, Japan, South Korea, Australia, Taiwan and Israel, as well as in some Central American countries, and is marketed in 21 countries worldwide.

For more information on BIAL's clinical development program of OPC till date (32 Phase I, 2 Phase II, 2 Phase III studies and 1 completed Phase IV study) to support the proposed use of OPC as adjunctive therapy to L-DOPA plus a DDCI in patients with PD who have motor fluctuations, reference is made to the OPC Investigator's Brochure.

A waiver (class waiver) to develop OPC in the paediatric population was granted by the European Medicines Agency (EMA) on 14 January 2011; on 26 May 2023, the Paediatric Committee issued a decision on the granting of a specific product waiver (EMEA-003406-PIP01-23).

In the EU, the approved therapeutic indication of OPC (*Ongentys* and *Ontilyv*) is as follows:

Ongentys is indicated as adjunctive therapy to preparations of levodopa / DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations. The usual recommended dose is 50 mg OPC once daily.

Now, with the addendum to the clinical modules, BIAL is seeking an extension of indication in the EU for OPC as an adjunctive therapy to preparations of L-DOPA/DDCI in adult patients for the treatment of signs and symptoms of Parkinson's disease without motor fluctuations.

Scientific advice concerning this extension of indication was sought from the EMA. BIAL requested scientific advice from the EMA on 15 May 2020, and advice was provided by the agency to BIAL on 23 July 2020. All of the advice provided has been addressed, as appropriate, including adaptation of study design. For details reference is made to SA report (EMEA/H/SA/2250/2/2020/II).

5.1.4. General comments on compliance with GCP

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations

[3] Stocchi F, Vacca L, Grassini P, Battaglia G, Onofrj M, Valente M, et al. Optimizing levodopa pharmacokinetics in Parkinson s disease: the role of COMT inhibitor. Archives of Orthopaedic and Trauma Surgery. 2003 Oct 21;24(3):217–8.

of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and other Guidelines, and applicable laws and regulations including the archiving of essential documents as well as the ethical principles of the Declaration of Helsinki.

The study interventions (OPC and matching placebo capsules) were manufactured in accordance with Good Manufacturing Practice, GCP guidelines and national/local legal requirements.

Study monitors (IQVIA) performed ongoing source data verification to confirm that data entered into the eCRF by authorised study centre personnel were accurate, complete, and verifiable from source documents; that the safety and rights of patients were being protected; and that the study was being conducted in accordance with the currently approved Study Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

5.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

5.2.1. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment for opicapone, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00)" has been submitted.

It is concluded that opicapone is not expected to pose any risk to the environment when used as stated in the SmPC.

Summary of study results:

Substance (INN/Invented Name): opicapone			
CAS-number (if available): 923287-50-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.16 (pH = 7.4)	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.16	No
	BCF	Not required	
Persistence	DT50 $_{\text{total system, 12°C}}$	525 d (river)	vP (in reference to ECHA, 2017, R 11)
Toxicity	NOEC or CMR	NOEC = 0.24 mg/L	not T
PBT-statement :	Opicapone is considered to be not PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC surfacewater, default	0.25	µg/L	> 0.01 threshold
Other concerns			N

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption, BIA 9-1067	OECD 121	Koc-soil < 17.8 Koc.sludge < 33.1	OECD 106 not feasible.
Ready Biodegradability Test, D 73805	OECD 301 B	0 %/ 28d not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, D73862	OECD 308	$DT_{50\ water}$ = 0.30 d (R), 0.46 (P) $DT_{50,\ total\ system}$ = 59.3 d (R), 246 d (P) (DFOP, k_2) % shifting to sediment = 82% % CO_2 (max) = 9.6 % NER (max) = 56.9 Transformation products Test duration: 40 d	20° C, R=River loamy sand P=Pond silt loam At day 11 At test end At test end No information available at test end

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata,* D73816	OECD 201	NOEC	240	µg/L	growth rate
Daphnia sp. Reproduction Test, D73827	OECD 211	NOEC	8800	µg/L	reproduction
Fish, Early Life Stage Toxicity Test/ *Danio rerio,* D73838	OECD 210	NOEC	3600	µg/L	Growth (length)
Activated Sludge, Respiration Inhibition Test, D73840	OECD 209 (2010)	NOEC	≥ 100	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism / *C. riparius*	OECD 219	NOEC	≥ 17,4	mg/ kg_{dw}	emergence, result normalised to

					10% organic carbon

5.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new indication does not lead to change in the outcome of the ERA. Opicapone is not expected to pose a risk to the environment.

5.3. Clinical aspects

5.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

5.3.2. Pharmacokinetics

N/A for this study. The pharmacokinetic properties and potential drug-drug interactions of OPC are anticipated to be the same in subjects with Parkinson's disease regardless of the presence or not of motor fluctuations. These characteristics of OPC are described in detail in the initial MAA.

5.3.3. Pharmacodynamics

N/A for this study.

5.3.4. PK/PD modelling

N/A for this study.

5.4. Clinical efficacy

5.4.1. Dose response study

N/A for this study.

The current approved and marketed EU-recommended dose of OPC is 50 mg QD at bedtime. Thus, this dose recommendation was chosen for evaluation in subjects with Parkinson's disease without signs of motor complications (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesia). OPC 50 mg should be taken at least 1 hour apart from L-DOPA/DDCI. The 50 mg dose and the timing relative to L-DOPA/DDCI were determined based on an initial series of Phase 1 and 2 studies, which provided a solid dose rationale for the doses to be tested in the Phase 3 studies in the initial MAA.

5.4.2. Main study

Title of the study

To explore the potential of OPC to enhance the clinical benefit of L-DOPA in L-DOPA / DDCI treated patients in the early stages of PD (patients without end-of-dose motor fluctuations, 'non fluctuators'), BIAL has carried out a dedicated Phase III double-blind, randomised, placebo-controlled and parallel-group study to evaluate the efficacy and safety of OPC as add-on to stable L-DOPA plus DDCI therapy in early idiopathic PD (The EPSILON Study: Early ParkinSon wIth L-DOPA/DDCI and OpicapoNe; Study BIA-91067-303, hereby referred to as Study 303).

The OPC clinical development programme included till date 32 Phase I studies, two Phase II studies and two Phase III and one completed Phase IV study which provided data to support the use of OPC as adjunctive therapy to combinations of L-DOPA/DDCI in patients with Parkinson's disease who have motor fluctuations. The results of the Phase 2 and Phase 3 clinical efficacy studies are included in the initial marketing authorisation application (MAA).

Overall, in clinical studies conducted so far, and including this latest study, OPC has been administered at any dose to a total of 3003 subjects: 1277 healthy subjects, 2397 subjects with PD and motor fluctuations and 177 subjects with PD without motor fluctuations (**Table 1**).

Table 1 – Summary of total exposure in the opicapone clinical programme (completed studies)

Development phase	Patient population	Number of studies	Number of subjects treated	
			OPC	Placebo
Phase 1	Adult healthy subjects[a]	38	1277	243
Phase 2	Adult subjects with Parkinson's disease and motor fluctuations	3	64	19
Phase 3 DB		2	631	257
Phase 3 OL (overall)		(2)[b]	848	0
Phase 3 OL (newly treated)		(2)[b]	320	0
Phase 3 DB	Adult subjects with Parkinson's disease, without motor fluctuations	1	177	178
Phase 4 OL	Adult subjects with Parkinson's disease and wearing-off motor fluctuations[d]	2	534	0
Total treated in clinical studies		46[b]	3003[c]	697

Source: ISDB (safety set).
CSR = clinical study report; DB = double-blind; ENT = entacapone; ISDB = Integrated Safety Database; OL = open-label; OPC = opicapone.
[a] Including hepatically impaired subjects in Study BIA-91067-106 and PD patients in Study NBI-OPC-1706.
[b] Counting the DB and OL periods of the Phase 3 studies as 1 study. Phase 3 studies include DB and OL periods.
[c] The total column only includes the 121 plus 99 subjects from the Phase 3 OL for Study 302 and Study 301 who were treated with placebo in the DB period and then with OPC in the OL period. Furthermore, this includes 100 subjects from the Phase 3 OL period of Study 301 treated with ENT in the DB period and then with OPC in the OL period.
[d] Data from Study BIA-OPC-401. This includes all subjects enrolled at all sites; however, the analysis in the CSR excludes data from site 211 due to major audit findings.
Notes: Studies sponsored by BIAL, ONO and Neurocrine.
Phase 1 studies include BIA-91067-101, -102, -103, -104, -105, -106, -107, -108, -109, -110, -111, -112, -113, -114, -115, -116, -117, -118, -119, -120, -121, -122, -123, -124, -125, -126, -127, -128, -129, -130, -131, -132, NBI-OPC-1705, -1706, -1707, -1708, ONO-2370-01, -03.
Phase 2 studies include BIA-91067-201, -202, -203.
Phase 3 studies include DB periods of Study 301, Study 302 and Study 303, and OL periods of Study 301 and Study 302.
Phase 4 studies include BIA-OPC-401, BIA-91067-402.

Data from studies ONO-2370-02, ONO-2370-05, NBI-OPC-1722, FSWB-PHI-OPC-1801 and OGT_001 are not integrated into the ISDB.

Methods

Study design

This was a Phase III, multicentre, double-blind (DB), placebo-controlled, parallel-group study to evaluate the efficacy and safety of OPC in patients with early idiopathic PD receiving treatment with L-DOPA plus a DDCI, and who were without signs of any motor complications (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesias).

This study was designed to include a double-blind (DB) period and open-label (OL) period. This report only covers the objectives and endpoints and the results of the DB period. The results of the OL extension period will be presented in a separate report. During the ongoing OL period of study 303, as of the cut-off date of up to 30th April 2023, 307 subjects had been exposed to OPC. All doses of OPC were given orally in the clinical studies (**Table 2**).

Table 2 - Overview of exposure in Study 303 (DB period + OL period up to 30 April 2023) and integrated Phase 3 studies

Study	Total number of subjects	
	Placebo	Total OPC[a]
303 DB period	178	177
303 OL period (up to 30 April 2023)	-	307
DB periods of Study 301 and Study 302 (combined)	257	631
DB periods of Phase 3 studies (Study 301, Study 302 and Study 303) (combined)	435	808

Source: Table 14.1.2.1, CSR Study 303 and ISDB (Safety Set).
DB = double-blind; OL = open-label; OPC = opicapone.
[a] Total OPC = OPC 5 mg + OPC 25 mg + OPC 50 mg.

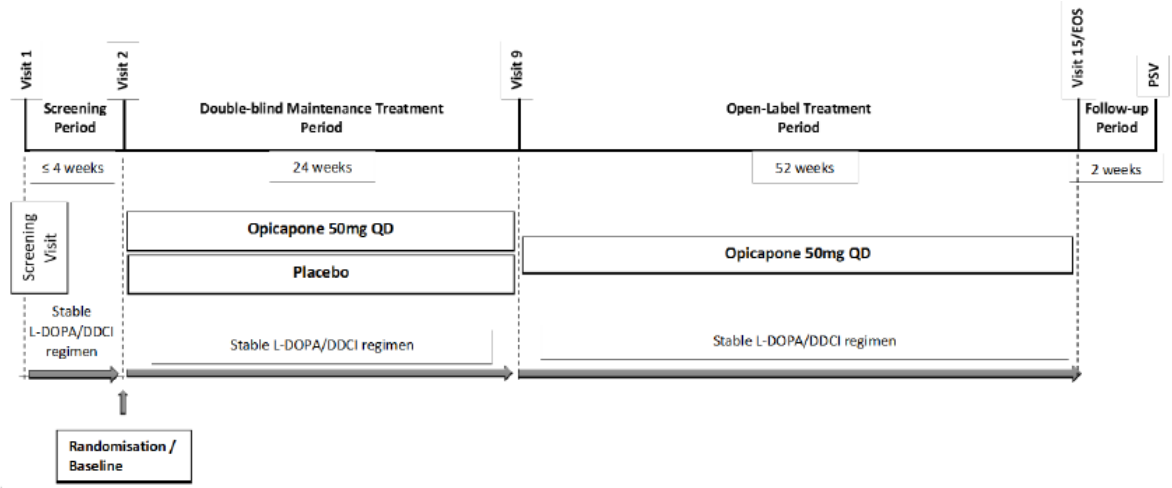
After a screening period of up to 4 weeks (Visit 1), at Visit 2 (DB baseline), eligible patients were randomly assigned to 1 of 2 treatment arms (OPC 50 mg or placebo) in a 1: 1 ratio, and entered a 24-week placebo-controlled, parallel-group, double-blind treatment period (Visits 2 to 9). Patients were assessed at 2 weeks and 4 weeks, and then at 4-week intervals either by telephone (Visits 5, 7, and 8) or at clinic visits (Visits 3, 4, 6, and 9). Visit 9 was considered as End-of-Study (EOS) visit for patients who do not continue into the OL period. A Post-study Visit (PSV) was performed approximately 2 weeks after the EOS visit or Early Discontinuation Visit.

Patients in this study had a diagnosis of early-stage PD with no motor complications; however, Wearing-off Questionnaire (WOQ-9) and Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part IV were to be used to follow the emergence of any motor complications.

A patient was considered to have completed the DB period of the study if he/she had completed all visits, up to and including Visit 9, and the PSV if they were not continuing in the OL extension period. For any missing visits, data rules were applied as described in the Statistical Analysis Plan (SAP).

Participant flow

A schematic presentation of study design is provided in the following figure.



DDCI = dopa decarboxylase inhibitor; EOS = End-of-Study Visit; L-DOPA = levodopa; PSV = Post-study Visit; QD = once daily.
Source: Appendix 16.1.1

Study participants

This study was conducted in 13 countries, where a total of 83 study centres were initiated and a total of 74 investigators at 74 study centres consented 1 patient or more.

Treatments

After a screening period of up to 4 weeks (Visit 1), at Visit 2 (DB baseline), eligible patients were randomly assigned to 1 of 2 treatment arms (OPC 50 mg or placebo) in a 1: 1 ratio, and entered a 24-week placebo-controlled, parallel-group, double-blind treatment period (Visits 2 to 9). Patients were assessed at 2 weeks and 4 weeks, and then at 4-week intervals either by telephone (Visits 5, 7, and 8) or at clinic visits (Visits 3, 4, 6, and 9). Visit 9 was considered as End-of-Study (EOS) visit for patients who do not continue into the OL period. A Post-study Visit was performed approximately 2 weeks after the EOS visit or Early Discontinuation Visit. Study treatment was administered in combination with the patient's usual L-DOPA/DDCI therapy. It was important that the patient received a stable regimen of L-DOPA/DDCI therapy for at least 4 weeks prior to Visit 2 and continued to remain at a stable dose throughout the DB period of the study unless dose adjustment was necessary for patient's safety.

Objectives / Outcomes / Endpoints

Primary objective: To evaluate the efficacy of once-daily 50 mg OPC as add-on to stable L-DOPA/DDCI therapy in patients with early-stage PD.

Primary endpoint: Change from baseline (Visit 2) to the end of the DB period (Visit 9) in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III total score.

Secondary objective: To evaluate the safety and tolerability of once-daily 50 mg OPC as add-on to stable L-DOPA/DDCI therapy in patients with early-stage PD.

Secondary Endpoints:

• Change from baseline (Visit 2) to post-baseline visits during the DB period in:

- MDS-UPDRS total scores: Parts I, II, III and IV, and Part II + III
- Modified Hoehn & Yahr staging total score
- Schwab and England scale score
- Parkinson's Disease Sleep Scale 2 (PDSS-2) total score
- Non-Motor Symptoms Scale (NMSS) total and subdomain scores
- Parkinson's Disease Questionnaire (PDQ-39) total and subdomain scores
- 9-item Wearing-off questionnaire (WOQ-9): Presence of wearing-off, total and sub-section (motor and non-motor) scores

• Proportion of patients with an improvement relative to their condition before the beginning of treatment in Clinical Global Impression of Improvement (CGI-I) total score at the end of the DB period at Week 24 (Visit 9).

• Proportion of patients with an improvement relative to their condition before the beginning of treatment in Patient's Global Impression of Improvement (PGI-I) total score at the end of the DB period – Week 24 (Visit 9).

- Treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs)
- Laboratory safety tests (biochemistry, haematology, and urinalysis)
- Physical and neurological examinations
- Vital signs
- 12-lead electrocardiogram (ECG) readings
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Modified Minnesota Impulsive Disorders Interview (mMIDI)

CHMP comment

The primary and secondary endpoints are in line with the EMA guideline on treatment of PD (EMA/CHMP/330418/2012 rev.2) and are accepted. The MDS-UPDRS Part III is a commonly accepted and validated used tool to measure progression in patients with Parkinson's disease, including non-motor aspects of experiences of daily living (Part I), motor aspects of experiences of daily living (Part II), motor examination (Part III) and motor complications (Part IV). The proposed primary endpoint - change from baseline to the end of the double-blind period in MDS-UPDRS Part III total score - is considered adequate to support the claim on symptomatic control and delaying the need for additional dopaminergic treatment. Change from baseline to the end of the double-blind period in MDS-UPDRS Part IV total score as a key secondary endpoint is acceptable.

Estimand

Primary estimand: The efficacy of once-daily 50 mg OPC as add-on to stable L-DOPA/DDCI therapy in patients with early-stage PD.

- Population: Patients with early-stage PD treated with L-DOPA/DDCI therapy, with no signs of motor complications (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesias). Refer to complete list of inclusion and exclusion criteria.
- Endpoint: Change from baseline (Visit 2) to the end of the double-blind period (Visit 9) in MDS-UPDRS Part III total score.
- Strategy for addressing intercurrent event: Hypothetical strategy followed assuming a subject who discontinues treatment prematurely follows the trend as if they had stayed on the randomized treatment. The strategy also assumes that post-conflict data (post 24FEB2022) for a Ukrainian subject will follow the trend in a conflict free scenario.
- Population-level summary: Estimated randomized treatment difference in mean change from double-blind baseline (Visit 2) to the end of the double-blind period (Visit 9).

CHMP comment

While a hypothetical strategy may be acceptable to target the effect in a conflict free scenario (for Ukrainian subjects), further discussion should be provided on why validity of data that were collected post conflict for Ukrainian subjects is negatively impacted justifying their exclusion from the analysis (which is the case when a hypothetical strategy is targeted). In contrast, a hypothetical strategy is not considered acceptable for treatment discontinuation and instead a treatment policy strategy should be applied targeting the effect regardless of treatment discontinuation. In this regard, the applicant should elaborate on whether data were collected post treatment discontinuation that can be included in the analysis. If yes, such an analysis should be provided applying a missing data handling approach aligned to the treatment policy strategy for remaining missing data. (**OC**)

Table 3 Primary and secondary estimands

Estimand	Label	Attributes			
		Population	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Primary	The efficacy of once-daily 50 mg OPC as add-on to stable L-DOPA/ DDCI therapy in patients with early-stage PD.	Patients with early-stage PD treated with L-DOPA/DDCI therapy, with no signs of motor complications (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesias). See full list of inclusion and exclusion criteria in protocol Sections 9.3.1 and 9.3.2	Mean change from baseline (Visit 2) to the end of the double-blind period (Visit 9) in MDS-UPDRS Part III total score.	Hypothetical strategy followed assuming a patient who discontinues treatment prematurely follows the trend as if they had stayed on the randomised treatment. The strategy also assumed that post-conflict data (post 24-Feb-2022) for a Ukrainian patient would follow the trend in a conflict-free scenario.	Estimated randomised treatment difference in mean change from baseline (Visit 2) to the end of the DB period (Visit 9).
Secondary (one estimand per endpoint)	The efficacy of once-daily 50 mg OPC as add-on to stable L-DOPA/ DDCI therapy in patients with early-stage PD on other parameters.	As per the primary.	• Mean change from baseline (Visit 2) to the end of the double-blind period (Visit 9) in: • MDS-UPDRS Part I total score • MDS-UPDRS Part II total score • MDS-UPDRS Part IV total score • MDS-UPDRS Part II + III total score • Schwab and England scale score • PDSS-2 total score	As per the primary.	As per the primary.
			• NMSS total and subdomain scores • PDQ-39 total and subdomain scores		
Secondary	The efficacy of once-daily 50 mg OPC as add-on to stable L-DOPA/ DDCI therapy in patients with early-stage PD on other parameters.	As per the primary.	WOQ-9: Presence of wearing-off, total and sub-section (motor and non-motor) scores at the end of the DB period (Visit 9).	While on treatment strategy for non-Ukrainian patients and censoring for Ukrainian patients where post-conflict data (post 24-Feb-2022) for a Ukrainian patient was considered off-treatment.	The number and percentage of patients with presence of wearing-off for each WOQ-9 symptom at each scheduled visit.
Secondary	To evaluate the effect of once-daily 50 mg OPC as add-on to stable L-DOPA/DDCI therapy on the symptoms in patients with early-stage PD.	As per the primary.	The Modified Hoehn & Yahr staging total score for patients at the end of the double-blind period (Visit 9).	While on treatment strategy for non-Ukrainian patients and censoring for Ukrainian patients where post-conflict data (post 24-Feb-2022) for a Ukrainian patient will be considered off-treatment.	Descriptive statistics of the changes in score in each arm at post-DB baseline visits.
Secondary (one estimand per endpoint)	To evaluate the effect of once-daily 50 mg OPC as add-on to stable L-DOPA/DDCI therapy on the symptoms in patients with early-stage PD.	As per the primary.	Proportion of patients with an improvement relative to their condition before the beginning of treatment in CGI-I scale, and proportion relative to their condition at admission in PGI-I at post-DB baseline visits during the double-blind period.	While on treatment strategy for non-Ukrainian patients and censoring for Ukrainian patients where post-conflict data (post 24-Feb-2022) for a Ukrainian patient will be considered off-treatment.	Estimated odds ratio for proportion of responders (very much improved, much improved, minimally improved) in each arm with an improvement at the end of the double-blind period (and corresponding 95% CI) from logistic regression analysis.

Abbreviations: CGI-I = Clinical Global Impression of Improvement; CI = confidence interval; DB = double-blind; DDCI = dopa decarboxylase inhibitor; ECG = electrocardiogram; L-DOPA = levodopa; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; NMSS = Non-Motor Symptoms Scale; mMIDI = modified Minnesota Impulsive Disorders Interview; OPC = opicapone; PD = Parkinson's disease; PDQ-39 = Parkinson's Disease Questionnaire; PDSS-2 = Parkinson's Disease Sleep Scale, Version 2; UPDRS = Unified Parkinson's Disease Rating Scale; WOQ-9 = Wearing-off Questionnaire.

Sample size

A minimum clinically relevant magnitude of effect in change from baseline (Visit 2) of MDS-UPDRS Part III (primary endpoint) between treatment arms (OPC versus Placebo) was expected to be at least 3-unit points (Hauser et al. 2011, Horváth et al. 2015).

For the purpose of this evaluation, previous data were checked to understand the variability of a population-like intended-to-treat (early PD patients) within this clinical study: 2 phase III studies (DB phase for BIA-91067-301 and BIA-91067-302) showed a standard deviation (SD) for the change from baseline of UPDRS Part III equal to 6.9 points approximately for a group of patients with early fluctuation < 1 year and no older than 80 years (population comparable as much as possible to early PD patients). Following conversion formula of Goetz et al (2012) to convert from UPDRS Part III score to MDS-UPDRS Part III score, the standard deviation for early PD patients in change from baseline (Visit 2) of MDS-UPDRS Part III was expected to be 8.3 points.

Therefore, to determine the sample size, the following specifications were used:

- Level of significance of 5%, two-sided
- A power of 90%
- **Mean treatment effect of OPC versus Placebo of 3 points**
- Standard deviation of population equal to 8.3 points
- Primary endpoint assumed to follow normal distribution and equal variance in both treatment groups.

Under the assumptions defined, a sample size of 162 patients in each treatment group (a total of 324 patients) was required. The sample size was calculated using PASS version 13 and it was also validated by repeating the calculations with nQuery Adviser version 7.0. As the primary analysis was conducted in all randomised patients according to DB-FAS, it was not necessary to increase the calculated sample size for withdrawals/dropout as all patients were to be included in the analysis including discontinuations. Finally, assuming a screening failure rate equal to 15 % then a total of approximately 382 patients had to be screened.

If patients were to discontinue from the study or from study treatment during the DB period due to SARS-CoV-2 restrictions, additional patients could be randomised on top of the planned sample size. The number of additional patients randomised were not to exceed the number of patients discontinuing the study or study treatment in relation to SARS-CoV-2 restrictions. Randomisation of additional patients was ultimately decided by the sponsor before any study lock had occurred.

CHMP comment

Sample size calculation is acceptable.

In the end more patients than planned were screened (410) and randomized (355). The Applicant is asked to further elaborate on this discrepancy. (**OC**)

Randomisation / Blinding

The study was randomised with a randomization ratio 1:1 to either OPC 50 mg or matching placebo and double-blind testing was used to minimize selection bias. The DB period was unblinded after database lock (dated 15 March 2023) for the purpose of data analyses. However, patients and study centres will remain blinded to their double-blind treatment until the end of the study.

CHMP comment

Acceptable

Statistical methods

For purposes of analysis, the following analysis sets were defined for the DB period.

- **Double-blind Enroled Set (DB-ENR):** Included all patients who signed the ICF before entering the DB-period.
- **Double-blind Randomised Set (DB-RND):** Included all patients in the DB-ENR Set who were randomised to study treatment.
- **Double-blind Safety Analysis Set (DB-SAF):** Included all patients in the DB-RND who received at least 1 dose of study treatment in the DB period.
- **Double-blind Full Analysis Set (DB-FAS):** All patients in the DB-RND who received at least 1 dose of study treatment and had completed at least 1 post DB-baseline (Visit 2) MDS-UPDRS Part III questionnaire. For DB-FAS, the intent-to-treat principle was preserved, despite the exclusion of patients randomised who did not take the study medication or did not complete a questionnaire, because the decision of whether or not to begin the treatment and study assessments or complete a questionnaire could not be influenced by knowledge of the assigned treatment, ie, the study treatment was blinded.
- **Double-blind Per Protocol Analysis Set (DB-PPAS):** Included all patients in the DB-FAS who did not experience any reason for exclusion during the DB period.

The primary analysis set for efficacy evaluations is the DB-FAS.

CHMP comment

Generally, the analysis should be based on all randomized patients in line with the ITT principle. It can be acceptable to exclude patients never receiving treatment as this is not influenced by treatment. However, patients not having any post-baseline assessments should not be excluded as this can be influenced by treatment (even in a double-blind study) and introduce bias. However, in this study only 2 patients were excluded due to not having any post-baseline assessments and, hence, this issue is not further pursued.

For the double-blind primary endpoint, change from double-blind baseline to the end of the double-blind period (Visit 9) for the MDS-UPDS Part III total score will be performed using MMRM with fixed effects for baseline, geographical region (Eastern Europe (EU), Eastern Europe (non-EU), Western Europe, Southern Europe), randomized treatment, visit, randomized treatment by visit interaction and baseline by visit interaction, and subject as a random effect. An unstructured Variance-co-variance matrix will be used. Missing data will not be imputed and handled through the missing at random assumption of the MMRM.

The robustness of the MAR assumption will be assessed through the primary sensitivity analysis. This analysis will apply a missing-not-at-random (MNAR) assumption, where the unobserved values are not assumed to follow those that were observed. As per the estimand, the post conflict data (post 24FEB2022) for a Ukrainian subject will follow the trend in a conflict free scenario, and thus will be exempt from the missing-not-at-random (MNAR) assumption applied in the sensitivity analysis. This will be applied using control-based multiple imputation with 100 imputations, where subjects discontinuing from the OPC treatment group will have their missing post withdrawal data imputed from

the same MAR-based imputation model estimated from only the placebo subjects. Therefore, after discontinuation, the OPC subjects will drift towards the mean response of the placebo group.

As a second sensitivity analysis, the primary analysis will be repeated including post conflict data.

To assess the subgroups in the context of the primary objective, the MMRM model described above will be repeated by subgroup. Furthermore, subgroup by treatment interactions will be evaluated. Results will be displayed in a Forrest plot. The following subgroups will assessed:

- Age (≤65 years, >65 years),
- Gender (Female, Male),
- Time since Parkinson's Disease diagnosis (years) at Screening (< 3 years, ≥3 years),
- Mean daily dose of L-DOPA (<400mg, ≥400mg)

Continuous secondary endpoints will be analysed similar to the primary endpoint. For binary endpoints, a logistic regression with randomized treatment included in the models will be used.

There will be no adjustments for multiple comparisons, as all secondary endpoints are considered exploratory.

CHMP comment

The primary analysis is an MMRM analysis based on the missing at random assumption. Data of Ukrainian subjects is set to missing post conflict (i.e. post 24 FEB 2022). The MMRM may be considered acceptable to target the primary hypothetical estimand, but likely results in overestimation of the treatment effect in case a treatment policy strategy is targeted for treatment discontinuation which is considered of higher regulatory relevance. Furthermore it is quite unusual to include region as a covariate when this was not used as a stratification factor for randomization.

Aside from this the assumed variance structure for the primary MMRM analysis is unclear. While use of subject as a random effect results in a compound symmetry variance structure of repeated measurements, it is also stated in the SAP that the Variance-covariance matrix will be unstructured. The Applicant is asked to clarify the variance structure assumed for repeated measurements and provide the SAS code used for the primary analysis. If a compound symmetry structure is fitted as a result of including a random subject effect, results of modelling an unstructured covariance matrix should be provided (e.g. using a repeated statement instead of a random statement in SAS PROC MIXED) and vice versa. (**OC**)

As stated above, the primary analysis likely results in an overestimation in case a treatment policy strategy is targeted for treatment discontinuation, which is considered of higher regulatory relevance. Hence, the conducted sensitivity analysis applying control-based multiple imputations for all missing data (except for post conflict data) is appreciated as it is better aligned to a treatment policy strategy for treatment discontinuation. However, the imputation follows a copy reference approach resulting in imputed profiles that slowly approach the placebo profile. As it is unclear whether this assumed slow loss of effect following treatment discontinuation is adequate, an additional and potentially more conservative sensitivity analysis should be provided that is based on the Jump to Reference (J2R) approach. Hence, to support robustness and as they are better aligned to targeting a treatment policy strategy for treatment discontinuation (which is considered of higher regulatory relevance), the following sensitivity analyses based on multiple imputation should be done. For these analyses each individual imputed dataset should be analysed with an ANCOVA for the primary endpoint using similar covariates as for the primary analysis.

-multiply impute all missing data (including those missing post conflict) as for the primary sensitivity analysis (i.e. copy reference imputation).

-multiply impute missing data (except those missing post conflict) based on the J2R approach and multiply impute data missing post-conflict based on the MAR assumption.

-multiply impute all missing data (including those missing post conflict) based on the J2R approach

-include post conflict data and multiply impute missing data as for the primary sensitivity analysis (i.e. copy reference imputation)

-include post conflict data and multiply impute missing data based on the J2R approach.

The MAH is asked to provide a comprehensive overview of the results for all conducted sensitivity analyses. (**OC**)

Since the effect regardless of treatment discontinuation is considered of higher regulatory relevance, the conducted and additional sensitivity analyses are considered more appropriate than the primary MMRM analysis which targets a less relevant estimand with respect to treatment discontinuation. In light of this the applicant should discuss results of which analysis should best be reflected in the SmPC. (**OC**)

While an analysis including post conflict data was provided and also supported efficacy, the company is asked to further elaborate on the impact the conflict had on the study and effect estimation. Information should also be provided on how many Ukrainian subjects were impacted by this and how many data of these subjects were set to missing for analysis. (**OC**)

Recruitment

Prospective approval of protocol deviations (PDs) to recruitment and enrolment criteria, also known as protocol waivers or exemptions, was not permitted.

Conduct of the study

Baseline data

A total of 410 patients were enrolled and 355 patients were randomised into the DB period in 1:1 ratio across the 2 treatment groups, with 177 patients randomised to receive OPC 50 mg once daily and 178 patients randomised to receive placebo. All 355 randomised patients received at least 1 study medication administration and 163 patients (92.1%) in the OPC 50 mg group and 159 patients (89.3%) in the placebo group completed the DB period.

Table 4 Overview of study design and treatment regimen for study 303

Study	Number of subjects randomised	Study design	Treatment regimen
303	355 subjects with idiopathic Parkinson's disease without fluctuations in the motor response and/or involuntary movements/dyskinesias; 177 to OPC 50 mg group and 178 to placebo group) (322 subjects completed the DB period; 163 in the OPC 50 mg group and 159 in the placebo group) Age: 32 to 80 years	DB, randomised, placebo-controlled and parallel-group study comparing OPC 50 mg and placebo, both administered with existing L-DOPA/DDCI treatment: • 4-week screening period; • 24-week DB period; • 52-week OL period[a]; • 2-week follow-up period (after DB period for subjects who did not continue to the OL period, or after the OL period)	DB period of 24 weeks: **OPC 50 mg group**: OPC 50 mg. **Placebo group**: matched placebo. Study treatment was taken orally QD in the evening at least 1 hour after the last daily dose of L-DOPA/DDCI. OL period of 52 weeks[a] OPC 50 mg orally QD in the evening at least 1 hour after the last daily dose of L-DOPA/DDCI.

Source: Tables 14.1.1.1 and 14.1. 2.1 and Section 9, CSR Study 303.
DB = double-blind; DDCI = dopa decarboxylase inhibitors; L-DOPA = levodopa; OL = open-label; OPC = opicapone; QD = once daily.
[a] The OL period is ongoing.

Main inclusion criteria

Patients had to be between 30 and 80 years of age, inclusive, diagnosed with idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria within the previous 5 years, with disease severity Stages 1 to 2.5 (according to the modified Hoehn & Yahr staging) and an MDS-UPDRS Part III score ≥20. Patients had been receiving treatment with L-DOPA/DDCI for at least 1 year, and at a stable regimen for at least 4 weeks prior to Visit 2, at a daily dose in the range 300 to 500 mg, 3 to 4 times a day, had signs of treatable motor disability but no signs of motor complications (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesias), and were naïve to COMT inhibitors.

Main exclusion criteria

Patients with non-idiopathic PD with signs of motor complications with a total MDS-UPDRS Part IV A+B+C score of greater than '0' or concomitant use of monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine and moclobemide) other than those for the treatment of PD or received treatment with prohibited medications COMT inhibitors (eg, entacapone, tolcapone), antiemetics with antidopaminergic action (except domperidone) or Duopa (carbidopa/levodopa intestinal gel) within the 4 weeks before screening were excluded from the study. Patients with past (within 1 year) or present history of suicidal ideation or suicide attempts were also excluded from the study.

Demographic characteristics were generally similar between the treatment groups. Most patients were males (64.8%), white (99.2%), with a median age of 65 years. Mean (±SD) of body mass index was 27.64 (±4.132) kg/m^2 and was similar between treatment groups (**Table** 5).

Table 5 – Demographics and other baseline characteristics – Study 303 (DB-SAF)

Characteristic	Placebo N=178	OPC 50 mg N=177	Total N=355
Age at screening (years)			
n	178	177	355
Mean (SD)	64.5 (9.55)	63.7 (9.50)	64.1 (9.52)
Range (min; max)	(42; 80)	(32; 80)	(32; 80)
Age-class, n (%)			
≤65years	86 (48.3)	95 (53.7)	181 (51.0)
>65 years	92 (51.7)	82 (46.3)	174 (49.0)
Gender, n (%)			
Male	121 (68.0)	109 (61.6)	230 (64.8)
Female	57 (32.0)	68 (38.4)	125 (35.2)
Race, n (%)			
White	177 (99.4)	175 (98.9)	352 (99.2)
Black or African American	0 (0.0)	1 (0.6)	1 (0.3)
Missing	1 (0.6)	1 (0.6)	2 (0.6)
BMI (kg/m^2)			
n	178	176	354
Mean (SD)	27.48 (3.945)	27.80 (4.318)	27.64 (4.132)
Range (min; max)	(19.2; 41.5)	(18.6; 46.6)	(18.6; 46.6)

Source: Table 14.1.4.1.1, CSR Study 303.
BMI = body mass index; DB-SAF = Double-blind Safety Analysis Set; max = maximum; min = minimum; OPC = opicapone; SD = standard deviation.
N = number of subjects in the DB-SAF; n = number of subjects with available data.

There were no notable differences between the OPC 50 mg and placebo groups with respect to baseline (Visit 2) disease characteristics. The median time since PD diagnosis was 3.05 years (OPC) and 2.84 years (placebo), respectively. The majority of patients (68.5%) had Stage 2 disease (modified Hoehn and Yahr Scale) at baseline (Visit 2) in both the OPC 50 mg (119 patients, 67.2%) and the placebo groups (124 patients, 69.7 %).

At baseline, the median daily dose of L-DOPA was 400 mg for both treatment groups, which 95 patients (53.7 %) in the OPC 50 mg treatment group received ⩾400 mg L-DOPA therapy versus 96 patients (53.9 %) in the placebo group. L-DOPA/DDCI therapy alone was the PD therapy at baseline for 73 patients (41.2 %) in the OPC 50 mg group versus 75 patients (42.1%) in the placebo group, while 104 patients (58.8 %) in the OPC 50 mg treatment group received more than one anti-PD therapy (such as dopamine agonists and monoamine oxidase B inhibitors) versus 103 patients (57.9 %) in the placebo group.

Numbers analysed

A total of 410 patients were enrolled and 355 patients (100.0 %) were randomised (177 patients in the OPC 50 mg group and 178 patients in the placebo group). Of the 355 patients randomised, 353 patients (99.4 %) were included in the DB-FAS (176 patients in the OPC 50 mg group and 177 patients in the placebo group) and received at least 1 study medication administration. The reason for exclusion from the DB-FAS for both patients was no post-DB baseline MDS-UPDRS Part III questionnaire.

A total of 14 patients (7.9%) in the OPC 50 mg group and 19 patients (10.7%) in the placebo group permanently discontinued the study medication. 163 patients (92.1%) in the OPC 50 mg group and

159 patients (89.3%) in the placebo group completed the DB period. The most common primary reasons for permanent study medication discontinuation during DB period were:

- Significant protocol deviation, reported for 6 patients (3.4%) in the OPC 50 mg group and 4 patients (2.2%) in the placebo group
- Withdrawal of consent, reported for 2 patients (1.1%) in the OPC 50 mg group and 4 patients (2.2%) in the placebo group
- Intolerable adverse event reported for no patients (0.0%) in the OPC 50 mg group and 4 patients (2.2%) in the placebo group
- Death for 1 patient (0.6%) from the OPC 50 mg group and 3 patients (1.7%) from the placebo group who died due to TEAEs, none of which was considered related to study medication.

Table 6 Analysis Set DB Period (DB Enroled Set)

	Statistic	Opicapone 50 mg N = 177	Placebo N = 178	Total N = 355
Double-blind Enroled Set	n			410
Screen failures	n			55
Double-blind randomised set	n	177	178	355
Double-blind Safety Analysis Set	n (%)	177 (100.0)	178 (100.0)	355 (100.0)
Patients included	n (%)	177 (100.0)	178 (100.0)	355 (100.0)
Patients excluded		0	0	0
Double-blind Full Analysis Set				
Patients included	n (%)	176 (99.4)	177 (99.4)	353 (99.4)
Patients excluded	n (%)	1 (0.6)	1 (0.6)	2 (0.6)
Did not receive a dose of study medication in DB period	n (%)	0	0	0
No post-DB baseline MDS-UPDRS Part III questionnaire	n (%)	1 (0.6)	1 (0.6)	2 (0.6)
Double-blind Per Protocol Analysis Set				
Patients included	n (%)	164 (92.7)	158 (88.8)	322 (90.7)
Patients excluded	n (%)	13 (7.3)	20 (11.2)	33 (9.3)
Did not receive a dose of study medication in DB period	n (%)	0	0	0
No post-DB baseline MDS-UPDRS Part III questionnaire	n (%)	1 (0.6)	1 (0.6)	2 (0.6)
Critical or major protocol deviation in DB period	n (%)	13 (7.3)	20 (11.2)	33 (9.3)

DB: Double-blind; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; n: number of patients.
Note: Percentages were based on the number of patients in the double-blind randomised set by treatment group. DB Baseline: The last non-missing measurement taken prior to the date study medication was first dispensed. Double-blind Enroled set: Patients who provided informed consent.

Double-blind Randomised Set: Randomised patients, classified as per randomised treatment.
Double-blind Safety Analysis Set: Randomised patients who took at least one dose of study medication in the Double-blind period.
Double-blind Full Analysis Set: Randomised patients who took at least one dose of study medication and completed a post-baseline MDS-UPDRS Part III questionnaire in the Double-blind period.
Double-blind Per Protocol Analysis Set: Randomised patients who took at least one dose of study medication, completed post-baseline an MDS-UPDRS Part III questionnaire in the Double-blind period, and who did not experience reasons for exclusion from the Double-blind Per Protocol Analysis Set.
Patients could have more than one reason for exclusion from the Double-blind Per Protocol Analysis Set. Source: Table 14.1.2.1.

CHMP comment:

Study 303 was a 24-week Phase III double-blind, placebo-controlled and parallel-group study in 355 randomised adult patients with Parkinson's disease treated with levodopa/DDCI (alone or in combination with other antiparkinsonian medicinal products) and without signs of motor complications as assessed by MDS-UPDRS part IV.

Claim of the study was to explore the potential of OPC to enhance the clinical benefit of L-DOPA in L-DOPA-treated patients in the early stages of PD.

Patients had disease severity stages 1 to 2.5 (modified Hoehn and Yahr), were treated with 3 to 4 daily doses of levodopa/DDCI at daily doses in the range of 300 to 500 mg and had signs of treatable motor disability assessed by MDS-UPDRS Part III.

The study design is generally acceptable. Main in- and exclusion criteria are considered adequate. The demographic characteristics were similar between treatment groups. Overall, baseline Parkinson's disease characteristics did not differ significantly between treatment groups for most characteristics. The patient population included in the study 303 represents the intended target population. The median time since Parkinson's disease diagnosis was approximately 2.9 years, with roughly half of subjects having been diagnosed less than 3 years before screening. The majority of subjects (around 68%) had Stage 2 disease at screening. Inclusion of patients treated with L-DOPA/DDCI at a stable regimen is agreed. Changes in L-DOPA mean daily dose throughout the DB period were small and there were no meaningful differences between treatment groups that might be expected to influence the outcome of the study or the interpretation of results. The proposal to use a minimum threshold score of the MDS-UPDRS part III at screening of at least 20 points is acknowledged.

Overall, the protocol deviations were not considered to have affected the interpretation of results or the conclusions regarding efficacy. Compliance with study drug was high (97.28 % for OPC and 98.38 % for Placebo), which is considered reassuring. The results in the per-protocol population were consistent with the primary analysis in the DB-FAS population.

It is agreed that taken into account that OPC is approved for the treatment of more severe patients with PD compared to the currently proposed target population, no considerable new issues should be expected to emerge from the safety perspective. Therefore, it is not considered necessary to expose 100 patients for 1 year, as required by the ICH-E1. In line with the EMA Guideline on clinical investigation of medicinal product in the treatment of Parkinson's disease (EMA/CHMP/330418/2012/rev.2), study of three months' duration is recommended to demonstrate efficacy in patients on L-DOPA+ with insufficient control of motor symptoms. Therefore, the proposed study duration and DB period of 24 weeks is considered adequate.

Results

Outcomes and estimation

The primary efficacy endpoint was the change from baseline to the end of the DB period in MDS UPDRS Part III total score. Secondary efficacy endpoints, considered exploratory, included the changes from baseline to post-baseline visits in the DB period in: MDS-UPDRS total scores for Parts I, II, III, and IV, and Parts II + III; modified Hoehn & Yahr staging total score; Schwab and England scale score; PDSS-2 total score; NMSS total and subdomain scores; PDQ-39 total and subdomain scores; the presence of individual symptoms, total and subsection (motor and non-motor) scores on the WOQ 9; and the proportion of subjects with improvement in CGI-I total score and PGI-I total score.

Primary efficacy analysis and outcomes

The mean DB baseline values in MDS-UPDRS Part III total score were similar for the OPC 50 mg group (32.7) and the placebo group (34.4). The estimated LS mean change from baseline (Visit 2) in MDS-UPDRS Part III total score at Week 24 (Visit 9) was **- 6.5** (95% CI: -7.9, -5.2) for the OPC 50 mg group and **- 4.3** (95% CI: -5.7, -3.0) for the placebo group, with a statistically significant mean treatment difference of **-2.2** (95% CI: -3.9, -0.5) in favour of OPC 50 mg (p=0.010) (**Table** 7)

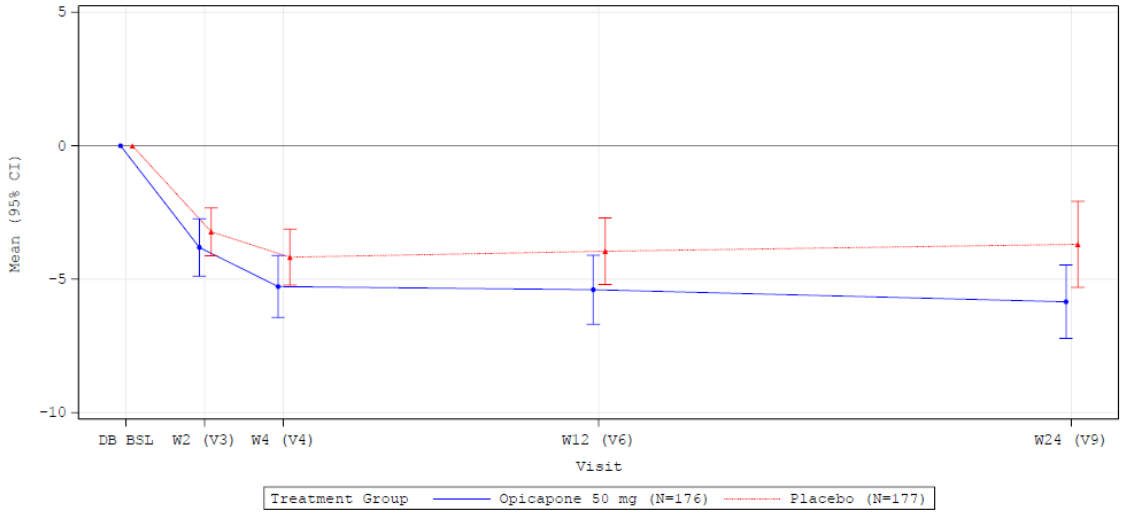
Table 7 Change in MDS-UPDRS Part III total score from baseline to endpoint (Week 24) – Study 303 (DB-FAS)

Statistic	Placebo N=177	OPC 50 mg N=176
DB Baseline		
n	177	174
Mean (SD)	**34.4** (11.70)	**32.7** (10.94)
Week 24		
n	144	145
Mean (SD)	**30.0** (14.13)	**27.2** (12.43)
Change from DB baseline to Week 24		
n	144	145
Mean (SD)	-3.7 (9.76)	-5.8 (8.38)
Estimates from MMRM		
LS mean (SE)	**-4.3** (0.68)	**-6.5** (0.69)
95% CI for LS mean	(-5.7, -3.0)	(-7.9, -5.2)
LS mean difference (SE)	**-2.2** (0.86)	
95% CI for difference in LS mean	(-3.9, -0.5)	
p-value	**0.010**	

Source data: Table 14.2.1.1, CSR Study 303.
CI = confidence interval; DB = double-blind; DB-FAS = double-blind Full Analysis Set; LS = least square; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMRM = mixed model for repeated measures; N = number of subjects treated; n = number of subjects with data; OPC = opicapone; SD = standard deviation; SE = standard error.
Note: DB baseline is the last non-missing measurement taken prior to the date study treatment is first dispensed. An MMRM approach was used to model change from DB baseline to Week 24 in MDS-UPDRS Part III, using DB baseline as covariate and categorical factors randomised treatment, region, visit, baseline by visit interaction, and randomised treatment by visit interaction, and subject as random effect. The significance level is 5% two-sided.

The mean change from baseline in MDS-UPDRS Part III total score for the OPC 50 mg group kept decreasing for every post-baseline visit through Week 24 (Visit 9), while in the placebo group the mean change from baseline in total score decreased through Week 4 (Visit 4) and then started to rebound towards DB-baseline. This slight divergence across time provided a near statistically difference at Week 12 (p=0.051) and later at Week 24 a statistically significant difference (p=0.010) in favour of OPC 50 mg over placebo (**Figure** 1**)**.

Figure 1 Mean Change from DB Baseline in MDS-UPDRS Part III Total Score: Observed Results by Treatment Group DBFAS



DB = Double-blind; BSL = baseline; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; N = Number of patients in the analysis set; CI = Confidence Interval.
DB Baseline = the last non-missing measurement taken prior to the date study medication is first dispensed.
Source: Table 14.2.2.1

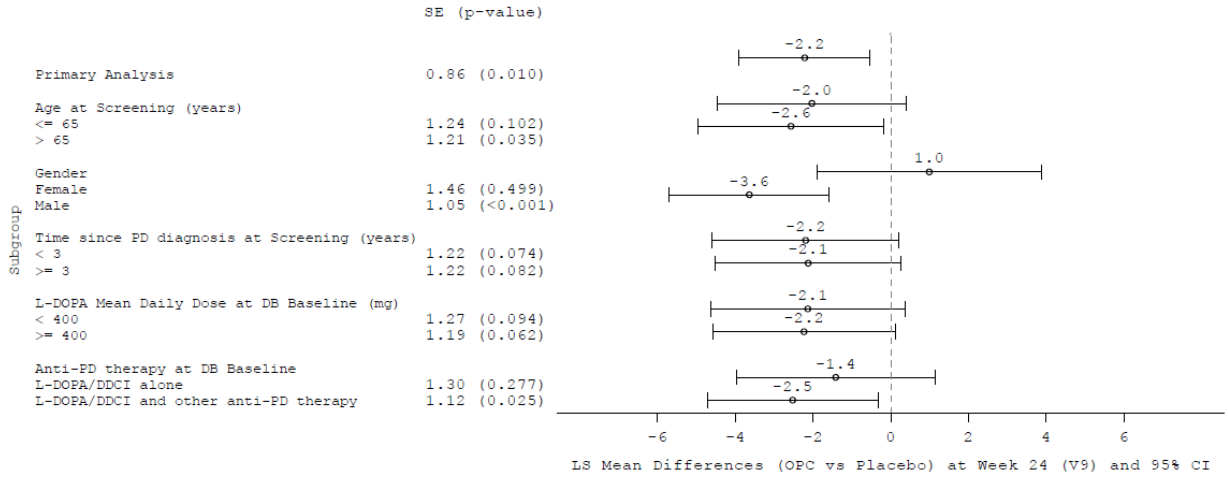
These results were consistent with the primary analysis in the DB Per Protocol Analysis Set using the same statistical analysis (LS mean treatment difference of - 2.6 points [95% CI -4.3, -0.8; p=0.004] in favour of OPC 50 mg).

Results of the sensitivity analysis using control-based imputations, and also including post-conflict data (Ukraine patients), also supported the results of the primary analysis in the DB-FAS population, demonstrating the robustness and consistence of the primary analysis. When using control-based imputation, the estimated LS mean change from baseline (Visit 2) was - 6.0 (95% CI: -7.5, -4.5) for the OPC 50 mg group and - 4.0 (95% CI: -5.4, -2.6) for the placebo group, with a statistically significant LS mean treatment difference in favour of the OPC 50 mg group compared with placebo of - 2.0 (95% CI: - 3.8, - 0.3; p=0.023). When including the post-conflict data of the Ukrainian study centres, the estimated LS mean change from baseline (Visit 2) was -6.4 (95% CI: -7.9, -4.9) for the OPC 50 mg group and -4.4 (95% CI: -5.9, -2.9) for the placebo group, with a statistically significant LS mean treatment difference in favour of the OPC 50 mg group compared with placebo of -2.0 (95% CI: - 4.0, 0.0; p=0.046) in favour of OPC 50 mg.

Exploratory subgroup analyses were conducted for the primary efficacy endpoint using the MAR assumption and showed the same trend of improvement for the change from baseline to Week 24 in the MDS-UPDRS Part III regardless of age, time since Parkinson's disease diagnosis, mean daily dose of L-DOPA and anti-Parkinson's disease therapy exposure at DB baseline.

Noteworthy, gender did not follow the same trend as all females showed a mean decrease in the MDS-UPDRS Part III Total Score from baseline to Week 24 in the OPC 50 mg group within the range of overall population and males; however, in the placebo group females showed at least two times higher mean decrease when compared with the overall placebo population and placebo males group, which provided a trend of improvement in favour of placebo over the OPC 50 mg within females (see **OC, LoQ**) (**Figure 2**).

Figure 2 Forest Plot of Treatment Effect for Change from DB Baseline to Week 24 (Visit 9) in MDS-UPDRS Part III



CHMP comment:

In early PD, clinical trials have defined "responders" as those improving by 20 % to 30 % in UPDRS total or motor scores, other studies have considered a mean change of at least 3 to 5 points on the UPDRS motor score as threshold to indicate that the minimal improvement of symptoms represents a clinically meaningful change from baseline. The minimal clinically important change (MCIC) of the unified PD rating scale appeared to increase slightly with increasing disease stages and a cut-off of 5 points remains appropriate for Hoehn and Yahr stages 1 to 3 (Schrag et al 2006, Stern et al 2004, Parkinson Study Group 1997, Hauser et al 2010).

In Study 303, the mean (±SD) MDS-UPDRS Part III total score at baseline (Visit 2) was similar for both groups, 32.7 (±10.94) for the OPC 50 mg group and 34.4 (±11.70) for the placebo group. The estimated LS mean change from baseline in MDS-UPDRS Part III total score at week 24 was - 6.5 (95% CI: -7.9, - 5.2) for the OPC 50 mg group and - 4.3 (95% CI: -5.7, -3.0) for the placebo group, with a statistically significant LS mean difference of - 2.2 (95% CI: -3.9, -0.5; p=0.010) for the comparison of OPC 50 mg group versus placebo (Table 7). The results in the DB-PPAS were consistent with the primary analysis in the DB-FAS (LS mean treatment difference of -2.6 points [95% CI -4.3, -0.8; p=0.004] in favour of OPC 50 mg). Notably, from baseline to week 4 a clinically meaningful change occurs also in the placebo group and then over time rebounds towards DB-baseline (Figure 1).

While conducted sensitivity analyses support these results, further analyses are necessary to substantiate the robustness of the data given that the primary analysis targets a less relevant estimand. The primary analysis rather overestimates the relevant effect and the reference based imputation analysis performed so far is not really a worst case scenario as the MAH repeatedly presents it (see statistical **OC, LoQ**).

Secondary endpoints (all analysed exploratory):

Secondary efficacy endpoints generally remained stable or showed small trends of improvement (mostly not significant) in favour of OPC 50 mg during the 24-week treatment period.

MDS-UPDRS Total Score

Part I: The baseline (Visit 2) values (mean ± SD) in MDS-UPDRS Part I total scores were similar for the OPC 50 mg group and placebo group (6.6 ± 4.58 vs 6.8 ± 4.99). Small LS mean changes from baseline (Visit 2) in the total mean scores to Week 24 (Visit 9) were observed for both treatment

groups, with no significant treatment differences (LS mean difference of 0.2; 95% CI: -0.5, 0.9; p=0.512).

Part II: The baseline (Visit 2) values (mean ± SD) in MDS-UPDRS Part II total scores were similar for the OPC 50 mg group and placebo group (9.1 ± 5.75 vs 9.1 ± 6.09). Small LS mean changes from baseline (Visit 2) in the total mean scores to Week 24 (Visit 9) were observed for both treatment groups, with no significant treatment differences (LS mean difference of -0.7; 95% CI: -1.5, 0.2; p=0.120).

Part IV: Since the patients enroled had early PD with no motor complications, baseline (Visit 2) scores were 0. At DB post-baseline visits, small mean increase in the scores were seen in both of the groups. This was a result of some patients rating motor complications in the DB post-baseline visits.

Parts II and III: Mean decreases were observed from baseline (Visit 2) through Weeks 4, 12, and 24 in both OPC 50 mg and placebo groups. The OPC 50 mg group had a statistically significant decrease (p=0.036) in the MDS-UPDRS Parts II + III total score at Week 24 (Visit 9) compared with the placebo group.

Table 8 Table Change in MDS-UPDRS Parts I, II, and IV, and II + III total scores from baseline to Week 24 – Study 303 (DB-FAS)

Statistic	Placebo N=177	OPC 50 mg N=176
MDS-UPDRS Part I total score		
DB Baseline		
n	177	174
Mean (SD)	**6.8** (4.99)	**6.6** (4.58)
Week 24		
n	144	145
Mean (SD)	6.5 (4.46)	6.7 (4.57)
Change from DB baseline to Week 24		
n	144	145
Mean (SD)	0.0 (3.42)	0.3 (3.90)
Estimates from MMRM		
LS mean (SE)	0.2 (0.28)	0.4 (0.28)
95% CI for LS mean	(-0.4, 0.7)	(-0.2, 1.0)
LS mean difference (SE)	0.2 (0.36)	
95% CI for difference in LS mean	(-0.5, 0.9)	
p-value	0.512	

Statistic	Placebo N=177		OPC 50 mg N=176
MDS-UPDRS Part II total scores			
DB Baseline			
n	177		174
Mean (SD)	**9.1** (6.09)		**9.1** (5.75)
Week 24			
n	145		145
Mean (SD)	9.0 (5.83)		8.5 (5.78)
Change from DB baseline to Week 24			
n	145		145
Mean (SD)	0.4 (3.71)		-0.4 (4.11)
Estimates from MMRM			
LS mean (SE)	0.3 (0.33)		-0.4 (0.34)
95% CI for LS mean	(-0.4, 0.9)		(-1.1, 0.2)
LS mean difference (SE)		-0.7 (0.44)	
95% CI for difference in LS mean		(-1.5, 0.2)	
p-value		0.120	
MDS-UPDRS Part IV total scores			
DB Baseline			
n	177		174
Mean (SD)	0.0 (0.38)		0.0 (0.00)
Week 24			
n	144		145
Mean (SD)	0.3 (1.11)		0.2 (0.83)
Change from DB baseline to Week 24			
n	144		145
Mean (SD)	0.3 (1.11)		0.2 (0.83)
Estimates from MMRM			
LS mean (SE)	0.4 (0.08)		0.3 (0.08)
95% CI for LS mean	(0.3, 0.6)		(0.1, 0.4)
LS mean difference (SE)		-0.1 (0.11)	
95% CI for difference in LS mean		(-0.3, 0.1)	
p-value		0.220	

Statistic	Placebo N=177	OPC 50 mg N=176
MDS-UPDRS Parts II + III total scores		
DB Baseline		
n	177	174
Mean (SD)	**43.5** (16.09)	**41.8** (15.13)
Week 24		
n	144	145
Mean (SD)	**39.0** (18.00)	**35.7** (16.50)
Change from DB baseline to Week 24		
n	144	145
Mean (SD)	-3.3 (11.67)	-6.2 (10.83)
Estimates from MMRM		
LS mean (SE)	**-4.6** (1.01)	**-7.4** (1.02)
95% CI for LS mean	(-6.6, -2.6)	(-9.4, -5.4)
LS mean difference (SE)	**-2.8** (1.31)	
95% CI for difference in LS mean	(-5.4, -0.2)	
p-value	**0.036**	

Source data: Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4, Table 14.2.2.5, CSR Study 303.
CI = confidence interval; DB = double-blind; DB-FAS = double-blind Full Analysis Set; LS = least square; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMRM = mixed model for repeated measures; N = number of subjects treated; OPC = opicapone; SD = standard deviation; SE = standard error.
Note: DB baseline is the last non-missing measurement taken prior to the date study treatment is first dispensed. An MMRM approach was used to model change from DB baseline to Week 24 in MDS-UPDRS total scores, using DB baseline as covariate and categorical factors randomised treatment, region, visit, baseline by visit interaction, and randomised treatment by visit interaction, and subject as random effect. The significance level is 5% two-sided.

Overall, for MDS-UPDRS Part I and Part II, small mean decreases (suggestive of improvement) were observed from baseline to Week 4 and Week 12 with OPC 50 mg. These changes were similar to those observed with placebo (non-significant treatment difference [p>0.05]) and returned to baseline values at Week 24 for both treatment groups.

With regards to the combination of Parts II + III, a mean decrease from baseline was observed at each post-DB baseline visit in both treatment groups. At Week 24, this estimated mean change from baseline in MDS-UPDRS Part II + III was statistically significantly larger with OPC 50 mg, with a mean difference to placebo of - 2.8 (p=0.036).

Subjects had MDS-UPDRS Part IV scores (motor complications) of 0 at DB baseline; a smaller LS mean increase in the change from baseline was seen with OPC 50 mg compared to placebo at Week 24, with no statistically significant difference between treatment groups (p=0.220).

Modified Hoehn and Yahr Staging

Based on modified Hoehn and Yahr staging, the majority of the patients at baseline (Visit 2) were at Stage 2 in the OPC 50 mg (65.5%) and the placebo group (73.4%) and this was generally maintained during the DB post-baseline visits through Week 24 (Visit 9). None of the patients progressed to Stage 4 or above.

Schwab and England Scale

There were no meaningful differences (mean ± SD) comparing the OPC 50 mg group with the placebo group in Schwab and England Scale scores at baseline through Week 24.

PDSS-2 Total Score

The mean scores for PDSS-2, that evaluates disease-related nocturnal disturbances, showed no improvement from baseline (Visit 2) at Week 24 (Visit 9) in either treatment group; however, the LS mean difference in the change from baseline (Visit 2) comparing the OPC 50 mg group (which did not get worse) with placebo (which got slightly worse) was statistically significant at Week 24 (p=0.039).

NMSS Total and Subdomain Scores

Overall, there were slight improvements in the NMSS total scores from baseline (Visit 2) through Week 24 (Visit 9) in both OPC 50 mg and placebo groups with no significant difference (p>0.05).

Similar results were observed in the subdomain scores except for Domain 7 (urinary). Significant improvements in urinary disturbances were observed in the OPC 50 mg group over placebo at Week 12 (p=0.0047) (Visit 6) and Week 24 (Visit 9) (p<0.001).

PDQ-39 Total and Subdomain Scores

Overall, the PDQ-39 total and subdomain scores showed slight improvements from baseline (Visit 2) through Week 24 (Visit 9) in both OPC 50 mg and placebo groups with no significant difference (p>0.05) between the two treatment groups.

WOQ-9 questionnaire

In the OPC 50 mg group, a slight increase from baseline (Visit 2) to Week 24 (Visit 9) in the proportion of patients with "Yes/Yes" (wearing off) was observed for tremor (from 62.1% to 65.5%) and cloudy mind/slowness of thinking (from 13.2% to 15.9%).

For the placebo group, a slight increase from baseline (Visit 2) to Week 24 (Visit 9) in the proportion of patients with "Yes/Yes" was observed for cloudy mind/slowness of thinking (from 7.9% to 12.4%) and pain/aching (15.8% to 17.2%)

All other signs and symptoms showed a slight decrease from baseline (Visit 2) to Week 24 (Visit 9) for both treatment groups.

CGI-I and PGI-I Scores

At Week 24 (Visit 9), according to Investigator assessment using the CGI-I scale, 50.3% of patients (73 patients) in the OPC 50 mg group showed improvement (minimally to very much improved) compared with 46.2% (67 patients) in the placebo group, with a response (improvement) odds ratio in favour of the OPC 50 mg group of 1.18 (95% CI: 0.74, 1.87; p=0.493), but not statistically significant.

At Week 24 (Visit 9), the proportion of patients with an improvement in the **PGI-I scores** (minimally to very much improved) was 57.9% (84 patients) in the OPC 50 mg group compared with 45.9 % (67 patients) in the placebo group, with a statistically significant response (improvement) odds ratio in favour of the OPC 50 mg group of 1.70 (95% CI: 1.06, 2.73; p=0.026), **Table** 9.

Table 9 Table Proportion of subjects with an improvement in CGI-I and PGI-I scores in the DB period – Study 303 (DB-FAS)

	Number of subjects (%)	
	Placebo N=177	**OPC 50 mg N=176**
CGI-I Score		
Week 24, n	145	145
Improvement	67 (46.2)	73 (50.3)
Very much improved	1 (0.7)	1 (0.7)
Much improved	15 (10.3)	24 (16.6)
Minimally improved	51 (35.2)	48 (33.1)
No improvement	78 (53.8)	72 (49.7)
Estimates from logistic regression		
Odds in favour of response	0.78	0.92
Odds ratio (95% CI) OPC vs. placebo	1.18 (0.74, 1.87)	
p-value	0.493	
PGI-I Score		
Week 24, n	146	145
Improvement	**67 (45.9)**	**84 (57.9)**
Very much improved	3 (2.1)	1 (0.7)
Much improved	16 (11.0)	27 (18.6)
Minimally improved	48 (32.9)	56 (38.6)
No improvement	79 (54.1)	61 (42.1)
Estimates from logistic regression		
Odds in favour of response	0.69	1.18
Odds ratio (95% CI) OPC vs. placebo	1.70 (1.06, 2.73)	
p-value	0.026	

Source data: Table 14.2.2.13 and Table 14.2.2.14, CSR Study 303.
CGI-I = Clinical Global Impression of Improvement; CI = confidence interval; DB = double-blind; DB-FAS = double-blind Full Analysis Set; N = number of subjects treated; n = number of subjects with available data; OPC = opicapone; PGI-I = Patient's Global Impression of Improvement.
Note: CGI-I scale measures the clinician's impression of the subject's improvement relative to their condition before the beginning of treatment. PGI-I scale measures the subject's assessment of their own condition relative to their condition at admission to the study.
An improvement is considered if the answer is "very much improved", "much improved" or "minimally improved".
A logistic regression model is used to model the proportion of subjects with an improvement from before treatment in CGI and PGI, using treatment and geographical region as fixed effects. The odds ratio displays how many times the odds of improvement for OPC is larger than the same odds for placebo.

CHMP Comment

Planning the sample size calculation of study 303 a minimum clinically relevant magnitude of effect in change from baseline of MDS-UPDRS Part III between treatment arms (OPC versus Placebo) was expected to be at least 3-unit points. The MAH has powered the study for a difference of 3 points from placebo and other studies in the literature have considered a mean change of at least 3 to 5 points as threshold to indicate that the minimal improvement of symptoms represents a clinically meaningful change. The treatment effect of OPC versus placebo appears rather moderate. The clinical relevance of the small difference seen in the primary analysis (i.e. 2.2 points, target was 3 points) between the groups needs to be further justified in light of the no/modest changes which are not reaching clinical

significance for the secondary endpoints (see **OC 10**). The MAH is asked to further substantiate that the observed improvements in the UPDRS score from baseline to the 6- month assessment correspond to clinically relevant changes in early stage PD patients. (**MO, LoQ**).

Notably, evaluating an additional efficacy outcome requires more power than the submitted study can provide. Considering the EMA guideline *Points to consider on application with one pivotal study (CPMP/EWP/2330/99)* the minimum requirement is generally one controlled study with statistically compelling and clinically relevant results. For study 303, the degree of statistical significance is considered sufficient (p=0.010) but the clinical relevance of the effect is questionable.

Analysis of subgroups

A moderate trend of improvement for the change from baseline to Week 24 in the MDS-UPDRS Part III was observed for OPC 50 mg compared to placebo, regardless of age, time since Parkinson's disease diagnosis, mean daily dose of L-DOPA and anti-Parkinson's disease therapy exposure at DB baseline. A statistically significant treatment effect ($p<0.05$) in favour of OPC 50 mg was associated with age at screening (subjects aged >65 years, p=0.035), gender (only for male subjects, $p<0.001$) and subjects taking L DOPA/DDCI with other anti Parkinson's disease therapy (p=0.025).

Noteworthy, all females showed a mean decrease in the MDS-UPDRS Part III Total Score from baseline to Week 24 in the OPC 50 mg group within the range of overall population and males; however, in the placebo group females showed at least two times higher mean decrease when compared with the overall placebo population and placebo males group, which resulted in a trend of improvement in favour of placebo over the OPC 50 mg treated females. The MAH is asked to further discuss the gender effect as female subjects showed a mean decrease in the UPDRS Part III total score in favour of placebo over OPC 50 mg due to a much higher placebo effect in females. The confidence intervals for the effect in females and men are barely overlapping (**Figure** 2**)** (**OC, LoQ**).

In general, the results for subgroups, age and region effects should be interpreted with caution with regard to the relative small number of patients within each subanalysis.

The short duration of study 303 is a critical limitation in early use of the disease. Therefore, the MAH is further asked to further justify the sustainability of the effect of opicapone while maintaining a constant levodopa dose beyond the study period of 24 weeks (**OC, LoQ**).

Supportive secondary efficacy endpoints generally remained stable or showed only small trends of improvement in favour of OPC 50 mg during the 24-week treatment period. Small but nominally statistically significant differences favouring opicapone were observed for nocturnal sleep disturbances (as assessed by the PDSS-2 total score), urinary symptoms (according to the NMSS, Domain 7) and PGI-I scores ((p=0.039, $p<0.001$, p=0.026, respectively). The mean scores for MDS UPDRS Part I and Part II showed also only moderate improvement from baseline with OPC 50 mg and with placebo during the 24 weeks of treatment, with no statistically significant difference between treatment groups. The low values of the scores indicating low disease burden at baseline hamper the possibility to show a treatment effect. Subject scores remained generally stable throughout the 24-week DB period in terms of Schwab and England scores and quality of life assessed by the PDQ-39 scale. Concerning the secondary endpoints, the clinical relevance of the observed treatment differences (OPC versus placebo) is questionable and needs to be further justified (**OC, LoQ**).

Summary of main study

The following **Table** 10 summarises the efficacy results from the main study supporting the present application which should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 Summary of Efficacy for trial BIA-91067-303

Title: A Phase III, Double-Blind, Randomized, Placebo-Controlled and Parallel-Group Study to Evaluate the Efficacy and Safety of Opicapone, as Add-on to Stable Levodopa (L-DOPA) Plus a Dopa Decarboxylase Inhibitor (DDCI) Therapy in Early Idiopathic Parkinson's Disease Patients, with an Open-Label Extension. The EPSILON Study Early ParkinSon wIth L-DOPA/DDCI and OpicapoNe		
Study identifier	Protocol Number: BIA-91067-303; EudraCT Number: 2020-005011-52	
Design	This is a pivotal Phase III, multicentre, double-blind (DB), placebo-controlled, parallel-group study to evaluate the efficacy and safety of Opicapone (OPC) in patients with early idiopathic Parkinson's Disease receiving treatment with L-DOPA plus a DDCI, and who are without signs of any motor complication (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesias). After a screening period of up to 4 weeks (Visit 1), eligible patients were randomly assigned to 1 of 2 treatment arms (OPC 50 mg or placebo) in a 1:1 ratio and entered a 24-week placebo-controlled, parallel-group, double-blind treatment period (Visits 2 to 9). Patients were assessed at 2 weeks and 4 weeks, and then at 4-week intervals either by telephone (Visits 5, 7, and 8) or at clinic visits (Visits 3, 4, 6, and 9). Visit 9 was considered an End-of-Study (EOS) visit for patients who do not continue into the open-label (OL) period. A Post-study Visit (PSV) was performed approximately 2 weeks after the EOS visit or Early Discontinuation Visit (EDV). Study treatment was administered in combination with the patient's usual L-DOPA/DDCI therapy. It was important that the patient received a stable regimen of L-DOPA/DDCI therapy for at least 4 weeks prior to Visit 2 and continued to remain at a stable dose throughout the DB period of the study unless dose adjustment was necessary for the patient's safety.	
	Duration of screening phase: Duration of double-blind treatment phase: Duration of extension phase:	4 weeks 24 weeks Up to 1 year
Hypothesis	Superiority:Explore the potential of OPC 50 mg compared against placebo, to enhance the clinical benefit of L-DOPA therapy as an add-on to stable L-DOPA/DDCI treatment for patients in the early stages of Parkinson's Disease (patients without end-of-dose motor fluctuations, "non-fluctuators".	
Treatments groups	OPC	Treatment: Opicapone 50 mg capsule, orally once daily in the evening at least 1 hour after the last daily dose of L-DOPA/DDCI. Duration: 24 weeks Number of randomized patients: 177 Number evaluated patients for efficacy (randomized and with available post-baseline data): 176

	Placebo	Treatment: Matching placebo will be taken orally once daily in the evening at least 1 hour after the last daily dose of L-DOPA/DDCI. Duration: 24 weeks Number of randomized patients: 178 Number evaluated patients for efficacy (randomized and with available post-baseline data): 177	
Endpoints and definitions	Primary efficacy endpoint	MDS-UPDRS Part III	Change from baseline (Visit 2) to the end of the double-blind period (Visit 9) in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor aspects of experiences of daily living assessed by the clinician) total score.
	Secondary efficacy endpoint	MDS-UPDRS Part I	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in MDS-UPDRS Part I (non-motor aspects of experiences of daily living assessed by the clinician) total score.
	Secondary efficacy endpoint	MDS-UPDRS Part II	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in MDS-UPDRS Part II (motor aspects of experiences of daily living assessed by the patient) total score.
	Secondary efficacy endpoint	MDS-UPDRS Part IV	Change from baseline (Visit2) to post-baseline visits during the double-blind period in MDS-UPDRS Part IV (motor complications) total score.
	Secondary efficacy endpoint	MDS-UPDRS Part II+III	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in MDS-UPDRS Part II+III total score.
	Secondary efficacy endpoint	Modified Hoehn & Yahr staging total score	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in Modified Hoehn & Yahr staging total score.
	Secondary efficacy endpoint	Schwab and England scale score	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in Schwab and England scale score.
	Secondary efficacy endpoint	NMSS total and subdomain scores	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in Non-Motor Symptoms Scale (NMSS) total and subdomain scores.
	Secondary efficacy endpoint	PDSS-2 total score	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in Parkinson's Disease Sleep Scale (PDSS-2).
	Secondary efficacy endpoint	PDQ-39 total and subdomain scores	Change from baseline (Visit 2) to post-baseline visits during the double-blind period in the Parkinson's Disease Questionnaire (PDQ-39) total and subdomain scores.

	Secondary efficacy endpoint	WOQ-9	Presence of wearing-off (proportion of patients), considering the total and sub-section (motor and non-motor) scores evaluated at baseline (Visit 2) and at the end of the DB period (Visit 9).
	Secondary efficacy endpoint	CGI-I total score	Proportion of patients with an improvement relative to their condition before the beginning of treatment in Clinical Global Impression of Improvement (CGI-I) total score at the end of the double-blind period at week 24 (Visit 9).
	Secondary efficacy endpoint	PGI-I total score	Proportion of patients with an improvement relative to their condition before the beginning of treatment in Patient's Global Impression of Improvement (PGI-I) total score at the end of the double-blind period at week 24 (Visit 9).
Database lock	15 March 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intended-to-treat The primary efficacy analysis was performed on the Double-blind Full Analysis Set (DB-FAS), which was defined as all patients in the Double-blind Randomised Set (DB-RND) set who received at least one dose of study medication in the double-blind period and completed at least one post-double-blind baseline MDS-UPDRS part III questionnaire. Treatment duration planned at the end of the double-blind period: Week 24 (visit 9)		
Descriptive statistics and estimate variability	Treatment group	OPC	Placebo
	Number of subjects	176	177
	MDS-UPDRS Part III Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	-6.5 (0.69) (-7.9, -5.2)	-4.3 (0.68) (-5.7, -3.0)
	MDS-UPDRS Part I Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	0.4 (0.28) (-0.2, 1.0)	0.2 (0.28) (-0.4, 0.7)
	MDS-UPDRS Part II Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	-0.4 (0.34) (-1.1, 0.2)	0.3 (0.33) (-0.4, 0.9)
	MDS-UPDRS Part IV Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	0.3 (0.08) (0.1, 0.4)	0.4 (0.08) (0.3, 0.6)

	MDS-UPDRS Part II+III Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)		-7.4 (1.02) (-9.4, -5.4)	-4.6 (1.01) (-6.6, -2.6)
	Modified Hoehn & Yahr staging total score Mean change from baseline do week 24 (Standard deviation)		-0.02 (0.249)	-0.03 (0.202)
	Schwab and England scale score Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)		0.0 (0.61) (-1.2, 1.2)	0.2 (0.61) (-1.0, 1.4)
	NMSS total and subdomain scores Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)		-1.4 (0.96) (-3.3, 0.4)	0.5 (0.96) (-1.4, 2.4)
	PDSS-2 total score Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)		0.0 (0.57) (-1.2, 1.1)	1.4 (0.57) (0.3, 2.5)
	PDQ-39 total and subdomain scores Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)		0.42 (0.622) (-0.80, 1.64)	0.69 (0.620) (-0.53, 1.90)
	WOQ-9 Proportion of patients	A slight increase from baseline (Visit 2) to Week 24 (Visit 9) in the proportion of patients with "Yes/Yes" (wearing off) was observed for tremor (from 62.1% to 65.5%) and cloudy mind/slowness of thinking (from 13.2% to 15.9%). Other symptoms showed a slight decrease from baseline (Visit 2) to Week 24 (Visit 9).	A slight increase from baseline (Visit 2) to Week 24 (Visit 9) in the proportion of patients with "Yes/Yes" was observed for cloudy mind/slowness of thinking (from 7.9% to 12.4%) and pain/aching (15.8% to 17.2%). Other symptoms showed a slight decrease from baseline (Visit 2) to Week 24 (Visit 9).	
	CGI-I total score The proportion of patients with any improvement at week 24		50.3%	46.2%
	PGI-I total score The proportion of patients with any improvement at week 24		57.9%	45.9%

Effect estimate per comparison	Primary endpoint **MDS-UPDRS Part III**	Comparison groups	OPC Placebo
		Difference between groups [LS Mean Diff. (SE)]	-2.2 (0.86)
		Confidence interval (95% CI for Diff. in LS Mean)	(-3.9, -0.5)

	P-value (Mixed model for repeated measures)	0.010
Secondary endpoint **MDS-UPDRS Part I**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	0.2 (0.36)
	Confidence interval (95% CI for Diff. in LS Mean)	(-0.5, 0.9)
	P-value	0.512
Secondary endpoint **MDS-UPDRS Part II**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-0.7 (0.44)
	Confidence interval (95% CI for Diff. in LS Mean)	(-1.5, 0.2)
	P-value	0.120
Secondary endpoint **MDS-UPDRS Part IV**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-0.1 (0.11)
	Confidence interval (95% CI for Diff. in LS Mean)	(-0.3, 0.1)
	P-value	0.220
Secondary endpoint **MDS-UPDRS Part II+III**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-2.8 (1.31)
	Confidence interval (95% CI for Diff. in LS Mean)	(-5.4, -0.2)
	P-value	0.036
Secondary endpoint	Comparison groups	OPC Placebo

Modified Hoehn & Yahr staging total score	Difference between groups [LS Mean Diff. (SE)]	N/A
	Confidence interval (95% CI for Diff. in LS Mean)	N/A
	P-value	N/A
Secondary endpoint **Schwab and England scale score**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-0.1 (0.76)
	Confidence interval (95% CI for Diff. in LS Mean)	(-1.6, 1.3)
	P-value	0.849
Secondary endpoint **NMSS total and subdomain scores**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-2.0 (1.21)
	Confidence interval (95% CI for Diff. in LS Mean)	(-4.4, 0.4)
	P-value	0.102
Secondary endpoint **PDSS-2 total score**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-1.5 (0.71)
	Confidence interval (95% CI for Diff. in LS Mean)	(-2.9, -0.1)
	P-value	0.039
Secondary endpoint **PDQ-39 total and subdomain scores**	Comparison groups	OPC Placebo
	Difference between groups [LS Mean Diff. (SE)]	-0.26 (0.774)
	Confidence interval (95% CI for Diff. in LS Mean)	(-1.78, 1.25)

		P-value	0.733
	Secondary endpoint **CGI-I total score**	Estimates from logistic regression	
		Odds in favour of response	0.92 (OPC) 0.78 (Placebo)
		Odds ratio (95% CI) OPC vs Placebo	1.18 (0.74, 1.87)
		P-value	0.493
	Secondary endpoint **PGI-I total score**	Estimates from logistic regression	
		Odds in favour of response	1.18 (OPC) 0.69 (Placebo)
		Odds ratio (95% CI) OPC vs Placebo	1.70 (1.06, 2.73)
		P-value	0.026
	Secondary endpoint **WOQ-9**	Comparison groups	OPC Placebo
		Difference between groups [LS Mean Diff. (SE)]	N/A
		Confidence interval (95% CI for Diff. in LS Mean)	N/A
		P-value	N/A

Notes

A total of 14 patients (7.9%) in the OPC group and 19 patients (10.7%) in the placebo group discontinued the study medications and were withdrawn early from the DB period. The most common primary reasons were:

Significant protocol deviation was reported for 6 patients (3.4%) in the OPC group and 4 patients (2.2%) in the placebo group. Withdrawal of consent was reported for 2 patients (1.1%) in the OPC group and 4 patients (2.2%) in the placebo group. Intolerable adverse events were reported for no patients in the OPC group and 4 patients (2.2%) in the placebo group. Death for 1 patient from the OPC group and 3 patients from the placebo group who died due to TEAEs, none of which was considered related to the study medication.

Exploratory subgroups analysis of the primary efficacy endpoint showed that regardless of age, time since Parkinson's disease diagnosis, mean daily dose of L-DOPA, and anti-Parkinson's disease therapy exposure at baseline, the mean decrease from baseline to Week 24 in the MDS-UPDRS Part III Total Score was observed for the opicapone and placebo groups with a favourable trend of improvement in favour of opicapone against placebo.

Overall, the protocol deviations were not considered to have affected the interpretation of results or the conclusions regarding efficacy. The results in the per-protocol population were consistent with the primary analysis in the DB-FAS population.

Primary Efficacy Analysis

The primary endpoint analysis included only patients with non-missing baseline data who belong to DB-FAS.

For the primary endpoint, change from DB baseline to the end of DB period for the MDS-UPDS Part III total score was performed using MMRM with fixed effects for DB baseline value, geographical region, randomised treatment, visit, randomised treatment by visit interaction and baseline by visit interaction, and patient as a random effect. The estimated treatment difference was present from the treatment by visit interaction using least square (LS) means, standard error (SE), 2-sided 95% CI, and associated p-values. Descriptive statistics were also calculated for the primary endpoint. The MMRM estimates of the treatment arms and observed values with 95% CI were also plotted graphically for each DB visit. The conduct of this analysis was pre-specified in the statistical analysis plan.

Sensitivity Analysis of Primary Endpoint

A sensitivity analysis of the double-blind primary endpoint was conducted to understand the impact of the missing data based on:

- Primary analysis using missing not at random with control base imputation instead of MAR, where unobserved data of the patients, independently of the randomised arm they belong to, were assumed to follow the distribution of non-missing patients in the Placebo group (worst-case scenario).
- Primary analysis adding Ukrainian data (post-conflict data, post 24 February 2022).

The conduct of this analysis was pre-specified in the statistical analysis plan.

Secondary Efficacy Analysis

Secondary efficacy analyses were to be considered exploratory only.

Opicapone 50 mg versus placebo was compared and presented as a mean effect difference with 95%Cis and associated p-values. For continuous secondary variables (MDS-UPDRS, Schwab and England scale, PDSS-2 total scores, NMSS domain and total scores PDQ-39 total and subdomain scores), the change from baseline to the post-baseline visits in the DB period was analysed and presented. Categorical (nominal) variables were summarised using the number and percentage of subjects. The conduct of this analysis was pre-specified in the statistical analysis plan.

Per-Protocol Primary Efficacy Analysis

A supplementary analysis was conducted for the primary endpoint using the Double-blind per-protocol population. This population included all patients in the DB-FAS who did not experience any reason for exclusion during the double-blind period. The conduct of this analysis was pre-specified in the statistical analysis plan.

Subgroup analysis

An exploratory subgroup analysis was conducted for the primary efficacy endpoint using the missing-at-random (MAR) assumption. This analysis was performed for different subgroups (age at screening, gender, time since Parkinson's disease diagnosis, mean daily dose of L-DOPA, and anti-Parkinson's disease therapy exposure at baseline) to investigate the consistency of the randomised treatment effects for different groups of patients. All categories in each subgroup used the same structure of covariance matrix, which was the minimal structure where all categories converged, following primary analysis modelling strategy. The conduct of this analysis was pre-specified in the statistical analysis plan.

5.4.3. Discussion on clinical efficacy

The purpose of this phase III study was to explore the potential of OPC to enhance the clinical benefit of L-DOPA/DDCI therapy being administered in early stage PD patients without motor fluctuations.

In study 303, mean change from baseline (Visit 2) in MDS-UPDRS Part III total score at the end of the DB period (Week 24 -Visit 9) using MMRM showed statistically significant improvement for the OPC 50 mg group over placebo with a LS mean difference of -2.2 (95% CI: -3.9, -0.5; p=0.010); thus, generally the efficacy hypothesis was met, with OPC at 50 mg once daily showing superiority compared with placebo in the improvement of motor signs and symptoms in PD patients without motor fluctuations after 24 weeks of treatment. However, the clinical relevance of these results appears questionable. The moderate treatment effect of OPC versus placebo and the clinical relevance of the small difference (i.e. 2.2 unit points, defined as target value was 3 points) between the groups needs to be further discussed and justified (**MO, LoQ**). It seems not clear if minor improvements of UPDRS score from baseline to the 6- month assessment correspond to clinically relevant changes in early stage PD patients.

The MAH is asked to further discuss the gender effect as female subjects showed a mean decrease in the UPDRS Part III total score in favour of placebo over OPC 50 mg due to a much higher placebo effect in females. The female placebo group showed at least twice time higher LS mean decrease (-8.8 ± 1.30) when compared with overall population (-4.3 ± 0.68) and males (-2.8 ± 0.80), which resulted in a trend of improvement in favour of placebo against the OPC 50 mg treated females. The confidence intervals for the effect in females and men are barely overlapping. (**Figure 2)** (**OC, LoQ**).

A short duration effect of OPC on outcome measures would be a critical limitation in early use of the disease. Therefore, the MAH is asked to further justify the sustainability effect of the UPDRS score improvement while maintaining a constant levodopa dose beyond the study period of 24 weeks (**OC, LoQ**).

Supportive secondary efficacy endpoints generally remained stable or showed only small and mostly not significant trends of improvement in favour of OPC 50 mg during the 24-week treatment period. For the PDSS-2 total score, OPC 50 mg group showed a small improvement of nocturnal sleep disturbances at Week 4 (Visit 4) and Week 12 (Visit 6) compared with the placebo group, while at Week 24 (Visit 9) the OPC 50 mg group showed a nominally statistically significant difference over placebo driven by a worsening in the placebo group (1.4; 95% CI: 0.3, 2.5) versus a stabilisation in the OPC 50 mg group (0.0; 95% CI: -1.2, 1.1). Indeed, nocturnal sleep disturbances (as assessed by the PDSS-2 total score) as well as urinary symptoms (according to the NMSS, Domain 7) remained stable with OPC 50 mg compared to placebo after 24 weeks of treatment ($p=0.039$ and $p<0.001$, respectively).

Regarding the MDS-UPDRS Part II (activity of daily life) and Part III total scores, the decrease of the mean change from baseline at Weeks 4 and 12 were higher in the OPC 50 mg group compared with the placebo group and a statistically significant LS mean difference at Week 24 was attained for OPC 50 mg compared with placebo ($p=0.036$). On the other hand, a smaller not significant increase in the change from baseline of MDS-UPDRS Part IV score (motor complications) was observed in the OPC 50 mg against placebo group at Week 24 (-0.1; 95% CI: -0.3, 0.1; $p=0.220$). The mean scores for MDS UPDRS Part I and Part II showed also only moderate improvement from baseline with OPC 50 mg and with placebo during the 24 weeks of treatment, with no statistically significant difference between treatment groups. Noteworthy, the low values of these scores indicating low disease burden at baseline hamper the possibility to show a treatment effect.

Subject scores remained generally stable throughout the 24-week DB period in terms of Schwab and England scores and quality of life assessed by the PDQ-39 scale with no meaningful differences for both treatment groups in the total and subdomain scores. Overall, there was a modest improvement in the proportion of patients with wearing-off assessed by WOQ- 9 questionnaire as well as in the non-motor symptoms total scores assessed by NMSS with no statistically significant difference at Week 24 for both treatment groups.

According to the clinical investigators (CGI-I) and the patients themselves (PGI-I), a greater proportion of patients experienced an improvement with OPC 50 mg (50.3% and 57.9%, respectively) compared to placebo (46.2% and 45.9%, respectively). The patient-reported improvement (PGI-I) was nominally statistically significant in favour of OPC 50 mg compared with placebo at Week 24, with an odds ratio of 1.70 (95 % CI: 1.06, 2.73; $p=0.026$).

Concerning the results of the secondary endpoints, the clinical relevance of the observed small treatment effects needs to be further justified (**OC, LoQ**).

5.4.4. Conclusions on the clinical efficacy

The OPC 50 mg group met the primary efficacy objective of superiority (p-value = 0.010) against the placebo group based on the mean change from baseline to week 24 in the MDS-UPDRS Part III total score. However, the treatment difference between OPC and the placebo group is small and the clinical relevance is therefore questionable.

The analyses of the secondary endpoints showed minimal to modest effects in favour of OPC 50 mg over placebo treatment, the mean change from baseline to Week 24 for MDS-UPDRS Part II + III and the improvements reported by the clinicians (CGI-I) and patients (PGI-I) were significantly better for OPC. OPC 50 mg was not associated with an increased development of motor complications when compared to placebo, as assessed by MDS-UPDRS Part IV. OPC 50 mg was also associated with a stabilization of the disease-related sleep disturbances, as assessed by the PDSS-2, in contrast with placebo.

Overall, the observed effects are small and do not clearly confirm the clinical benefit of OPC 50 mg as adjunctive therapy to L-DOPA/DDCI in the extended indication of adult early stage PD patients without motor fluctuations.

5.5. Clinical safety

Introduction

The safety of OPC 50 mg in subjects with Parkinson's disease without motor fluctuations was assessed by the pivotal Phase 3 study (Study 303). The support of the long-term safety of OPC was provided within the initial MAA, which contributes with about 68 % of the total safety population. Integrated safety information derives from DB period of all completed phase 3 studies (301, 302, 303) along with post-marketing surveillance information of over 6 years of worldwide marketing exposure. See **Table 1**, Section 5.4.2, Summary of total exposure in the opicapone clinical programme (completed studies)

In Study 303, the double-blind Safety Analysis Set (DB-SAF) contained all subjects who provided informed consent for the study, were randomised to receive study treatment, and took at least one dose of study treatment in the DB period. Subjects were classified according to the treatment they received and categorised in the actual treatment arm if they received at least one dose of study treatment. For the DB period, all outputs for safety outcomes were based on the DB-SAF data for the period, and baseline if mentioned referred to the DB baseline.

An overview of TEAEs reported during the DB period of Study 303 is presented in the following Table.

Table 11 – Overview of TEAEs – Study 303 (DB-SAF)

Type of event	Number (%) of subjects		
	Placebo N=178	OPC 50 mg N=177	Total N=355
Any TEAE	**84 (47.2)**	**84 (47.5)**	**168 (47.3)**
Any TEAE of special interest[a]	**12 (6.7)**	**13 (7.3)**	**25 (7.0)**
Any related TEAE	24 (13.5)	18 (10.2)	42 (11.8)
Any TESAE	5 (2.8)	9 (5.1)	14 (3.9)
Any severe TEAE	4 (2.2)	6 (3.4)	10 (2.8)
Any TEAE leading to death	3 (1.7)	1 (0.6)	4 (1.1)
Any TEAE leading to interruption of study treatment	4 (2.2)	1 (0.6)	5 (1.4)
Any TEAE leading to study treatment withdrawal	7 (3.9)	2 (1.1)	9 (2.5)

Source data: Table 14.3.1.1.1, CSR Study 303.
DB-SAF = double-blind Safety Analysis Set; N = number of subjects in the DB-SAF; OPC = opicapone; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
[a] Disease-related events such as motor fluctuations and dyskinesias.
Notes: For the DB period, TEAEs were defined as AEs that started or worsened on or after the date the study treatment was first dispensed and before the study treatment end date. Related TEAEs were defined was TEAEs with a relationship to study treatment as 'definitely related', 'probably related' or 'possibly related'; TEAEs with a relationship to study treatment as 'unlikely related' or 'not related' were defined as 'not related' TEAEs.
Subjects with more than one TEAE were counted once in the maximum severity and relationship categories; worst-case severity or relationship were reported. Missing severity or relationship to study treatment were classified as severe or related respectively.

The proportion of patients experiencing at least one TEAE was similar (< 5.0 % difference) between the OPC 50 mg group (84 patients, 47.5%) and the placebo group (84 patients, 47.2%). Overall, the incidence of study medication related TEAEs was low but similar in the OPC 50 mg group (18 patients, 10.2%) and the placebo group (24 patients, 13.5%).

Severe TEAEs were reported in 6 patients (3.4%) in the OPC 50 mg group versus 4 patients (2.2 %) in the placebo group. Of these, only 1 TEAE of fatigue in the OPC 50 mg group was considered related to study medication. The remaining study medication related TEAEs were mild or moderate in severity.

The overall incidence of TEAEs of special interest was similar between treatment groups (13 patients, 7.3 % for OPC 50 mg group; 12 patients, 6.7% for placebo group). The most common TEAEs of special interest were on-and-off phenomenon (13 patients, 3.7%), dyskinesia (7 patients, 2.0%), and tremor (9 patients, 2.5%).

Four patients (1.1%) died due to TEAEs during the DB period: 1 patient (0.6%) in the OPC 50 mg group (patient aged 66 years experienced severe cardio-respiratory arrest on DB Study Day 138) and 3 patients (1.7 %) in the placebo group (1 patient aged 77 years with COVID-19 and severe cardiopulmonary failure, one subject aged 76 years with sepsis and severe cardiac arrest, one subject aged 79 years with severe cardiopulmonary failure). None of the fatal AEs were considered related to study treatment.

Three deaths occurred during the ongoing OL period of Study 303 as of the cut-off date of 30 April 2023 (data on file); the events leading to death were assessed as not related to OPC 50 mg for all subjects. One male subject experienced sudden death, one male subject experienced Clostridium difficile sepsis and the cause of death for a female subject was acute respiratory distress syndrome associated with acute necrotising pancreatitis (the subject had taken the last dose of OPC 50 mg approximately a month and a half prior to death, when hospitalised for acute necrotising pancreatitis, and had been withdrawn from the study due to that event).

Nine patients (5.1%) in the OPC 50 mg group and 5 patients (2.8%) in the placebo group experienced serious TEAEs during the DB period. No treatment-related SAEs were reported in the OPC 50 mg group. One patient (0.6%) in the placebo group was reported with a serious TEAE of psychotic symptom, which was considered related to study intervention.

Two patients (1.1%) in the OPC 50 mg group and 7 patients (3.9%) in the placebo group were reported with TEAEs leading to permanent withdrawal of study medication. All events occurred as single occurrences except nausea, which was reported in 1 patient each in the OPC 50 mg and placebo groups.

In Study 303, which enrolled subjects without motor fluctuations, the TEAEs reported for ≥2.0% of subjects on OPC 50 mg vs placebo were COVID-19, on and off phenomenon, back pain and tremor (8.5% vs. 4.5%, 4.5% vs. 2.8%, 4.5% vs. 1.1% and 1.1% vs. 3.9% of subjects, respectively); dyskinesia, constipation, dry mouth and insomnia were reported for 1.7% vs. 2.2%, 1.7% vs. 0.6%, 1.1% vs. 0.0% and 2.3 % vs. 0.6 % of subjects, respectively (**Table 13**).

Table 12 – Incidence of TEAEs reported for ≥2.0% of subjects in either treatment group by PT, by SOC and PT – Study 303 (DB-SAF)

SOC PT	Placebo N=178 n (%)	OPC 50 mg N=177 n (%)	Total N=355 n (%)
Any TEAE	**84 (47.2)**	**84 (47.5)**	**168 (47.3)**
Nervous System Disorders	**29 (16.3)**	**24 (13.6)**	**53 (14.9)**
On and off phenomenon	5 (2.8)	8 (4.5)	13 (3.7)
Tremor	7 (3.9)	2 (1.1)	9 (2.5)
Dyskinesia	4 (2.2)	3 (1.7)	7 (2.0)
Dizziness	4 (2.2)	2 (1.1)	6 (1.7)
Headache	5 (2.8)	1 (0.6)	6 (1.7)
Infections and Infestations	**23 (12.9)**	**28 (15.8)**	**51 (14.4)**
COVID-19	8 (4.5)	15 (8.5)	23 (6.5)
Upper respiratory tract infection	4 (2.2)	1 (0.6)	5 (1.4)
Urinary tract infection	0 (0.0)	4 (2.3)	4 (1.1)
Musculoskeletal and Connective Tissue Disorders	**14 (7.9)**	**18 (10.2)**	**32 (9.0)**
Back pain	2 (1.1)	8 (4.5)	10 (2.8)
Arthralgia	5 (2.8)	4 (2.3)	9 (2.5)
Gastrointestinal Disorders	**18 (10.1)**	**12 (6.8)**	**30 (8.5)**
Nausea	3 (1.7)	4 (2.3)	7 (2.0)
Vomiting	5 (2.8)	0 (0.0)	5 (1.4)
General Disorders and Administration Site Conditions	**13 (7.3)**	**14 (7.9)**	**27 (7.6)**
Fatigue	4 (2.2)	5 (2.8)	9 (2.5)
Oedema peripheral	2 (1.1)	4 (2.3)	6 (1.7)
Psychiatric Disorders	**12 (6.7)**	**14 (7.9)**	**26 (7.3)**
Insomnia	1 (0.6)	4 (2.3)	5 (1.4)
Vascular Disorders	**6 (3.4)**	**10 (5.6)**	**16 (4.5)**
Hypertension	2 (1.1)	5 (2.8)	7 (2.0)
Injury, Poisoning and Procedural Complications	**8 (4.5)**	**6 (3.4)**	**14 (3.9)**
Fall	3 (1.7)	4 (2.3)	7 (2.0)

Source: Table 14.3.1.2.1, CSR Study 303.
AE = adverse event; COVID-19 = coronavirus disease 2019; DB = double-blind; DB-SAF = Double-blind Safety Analysis Set; MedDRA = Medical Dictionary for Regulatory Activities; OPC = opicapone; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

N = number of subjects in the DB-SAF; n = number of subjects with events.

Notes: For the DB period, TEAEs were defined as AEs that started or worsened on or after the date the study treatment was first dispensed and before the study treatment end date.

Subjects with more than one event within a SOC or PT were counted only once for that SOC or PT.

Adverse events were coded using MedDRA version 25.1.

No new clinically relevant trends were observed in the OPC 50 mg group for clinical laboratory assessments, including haematology, serum chemistry, or urinalysis. No trends were observed in other safety assessments, including vital signs, physical and neurological examination, ECG parameters, C-SSRS, and mMIDI.

To conclude, in study 303, the only related TEAEs leading to permanent discontinuation of study treatment in subjects on OPC 50 mg were nausea (in 1 subject) and illusion, vertigo and fall (in another subject). None of the deaths in the DB period of this study (including the single death in the

OPC 50 mg group) were assessed as related to study treatment. In the integrated population of all Phase 3 studies, dyskinesia was the most frequently reported related TEAE leading to permanent discontinuation of study treatment in subjects on OPC. The only death assessed as related to OPC in the Phase 3 studies was cerebral haemorrhage after traumatic brain injury due to a fall during the OL period of Study 302. During Study 303, a single TESAE was assessed as related to study treatment (PT: psychotic symptom, reported for a subject on placebo). There was no difference in the incidence of TESAEs assessed as related to OPC between the integrated population of Study 301 and Study 302 and the integrated population of all Phase 3 studies; no TESAEs were assessed as related to OPC treatment. In Study 303, a single severe TEAE of fatigue was assessed as related to OPC 50 mg. Otherwise, the incidence of severe TEAEs was low, with dyskinesia reported as the most frequent severe TEAE in the integrated population of all Phase 3 studies.

Comparison of safety analyses

Integrated analysis of DB periods of all Phase 3 studies confirmed the results of integrated analysis of DB periods of Study 301 and Study 302, with a greater proportion of subjects on OPC (25 and 50 mg) than on placebo experiencing TEAEs and related TEAEs, and a similar proportion of subjects experiencing TESAEs, severe TEAEs and TEAEs leading to premature discontinuation on both treatments. Integration of data from Study 303 during which similar proportions of subjects experienced TEAEs and related TEAEs on OPC 50 mg and placebo did not change the overall trend. As in the integrated populations, a similar proportion of subjects on OPC 50 mg and placebo experienced TESAEs, severe TEAEs and TEAEs leading to discontinuation during Study 303 (**Table 14**).

Table 13 – Overview of TEAEs – integrated analysis of DB periods of Phase 3 studies (Safety Set)

	Integrated Studies 301 and 302		Integrated Studies 301, 302 and 303			
	Placebo N=257	Total OPC 25 and 50 mg N=509	Placebo N=435		Total OPC 25 and 50 mg N=686	
	n (%)	n (%)	n (%)	e	n (%)	e
Deaths	1 (0.4)	0 (0.0)	4 (0.9)	6	1 (0.1)	1
At least one SAE	12 (4.7)	19 (3.7)	N/A	N/A	N/A	N/A
At least one TESAE	11 (4.3)	18 (3.5)	16 (3.7)	24	27 (3.9)	29
Premature discontinuation due to TEAE	18 (7.0)	36 (7.1)	25 (5.7)	36	38 (5.5)	62
At least one TEAE	147 (57.2)	322 (63.3)	231 (53.1)	602	406 (59.2)	1273
At least one severe TEAE	16 (6.2)	27 (5.3)	20 (4.6)	34	33 (4.8)	47
At least one related TEAE	75 (29.2)	212 (41.7)	99 (22.8)	181	230 (33.5)	514
Without any TEAE	110 (42.8)	187 (36.7)	204 (46.9)	-	280 (40.8)	-

Source: Table 2.7.4.AE.1.2, initial Module 2.7.4, Table AE.1.3, Table AE.2.3, Table AE.3.3, Table AE.5.3, Table AE.6.3, Table AE.14.3.
DB = double-blind; IMP = investigational medicinal product; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not available; OPC = opicapone; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
e = number of events; N = number of subjects in the Safety Set; n = number of subjects with events.
Notes: Relationship to IMP was reported as "possible", "probable", "definite" or missing.
Death was defined as a fatal outcome of an SAE.
The AEs were coded using MedDRA version 14.0 (Study 301) and version 16.0 (Study 302). For Study 303 and the integrated analysis of all Phase 3 studies, version 25.1 was used.

To classify the frequency of adverse reactions across the DB periods of all Phase 3 studies, all related TEAEs reported for subjects on opicapone (25 and 50 mg) with incidence rates higher than placebo and occurring in > 2 subjects on opicapone were categorised as very common (≥1/10), common (≥ 1/100

to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000); those with a known frequency are presented in **Table 15.**

Table 14 – Frequency of ADRs – integrated analysis of DB periods of Phase 3 studies (Safety Set)

SOC	PT		
	Very common	**Common**	**Uncommon**
Gastrointestinal Disorders	None	Constipation, dry mouth, nausea	Abdominal pain, abdominal pain upper, dyspepsia, vomiting
General Disorders and Administration Site Conditions	None	None	Fatigue
Injury, Poisoning and Procedural Complications	None	None	Fall
Investigations	None	Blood creatinine phosphokinase increased	Weight decreased
Musculoskeletal and Connective Tissue Disorders	None	None	Myalgia, muscle spasms
Nervous System Disorders	Dyskinesia	Dizziness, headache, somnolence	Dysgeusia
Psychiatric Disorders	None	Abnormal dreams, hallucination, insomnia	Anxiety, hallucination auditory, hallucination visual
Vascular Disorders	None	Orthostatic hypotension	Hypertension, hypotension

Source: Table AE.3.3.
ADR = adverse drug reaction; DB = double-blind; PT = Preferred Term; SOC = System Organ Class.

Comparing the currently approved section 4.8 of the SmPC with **Table 15**, the list of ADR terms in the integrated analysis of Study 301, Study 302 and Study 303 is shorter than the ADR list included in the SmPC. The MAH proposes to maintain the ADR terms in the SmPC as they are, in a conservative approach and considering the safety information from long-term post marketing surveillance.

The frequency of the ADRs simultaneously present in the Integrated Safety Database (ISDB) and the SmPC is the same, except for the events of 'vomiting', 'muscle spasms' and 'hallucination visual', earlier categorised as "common" in the current SmPC. These would now be categorised as "uncommon"; however, considering the conservative approach described above, as per MAH decision, these events have been retained in the "common" frequency.

All ADRs identified in Table 15 are considered expected as per the approved SmPC except for two ADRs ("fall" and "fatigue") with frequency higher in subjects on OPC than on placebo in the newly integrated safety analysis; the MAH proposes to include both ADRs in the revised SmPC (frequency "uncommon").

CHMP comment:

The safety analysis set provided by the MAH is considered acceptable. The population exposed to OPC and the duration of exposure is considered sufficiently large to detect AEs of reasonable frequency (0.5 – 5 %) and to elucidate, whether frequently occurring AEs increase or decrease over time. The exposure meets the recommendations in the *Note for Guidance on Population Exposure* (CPMP/ICH/375/95).

The SOCs reported most frequently (for > 10.0 % of subjects overall) were Nervous System Disorders and Infections and Infestations, reported at a similar incidence in the OPC 50 mg and placebo groups (13.6 % vs. 16.3% and 15.8% vs. 12.9%, respectively). The most commonly reported TEAEs (for > 3.0 % of subjects in any treatment group by PT) were reported at a similar incidence (< 5.0% difference) in both treatment groups and included coronavirus disease 2019 (COVID-19), on and off

phenomenon, back pain and tremor (8.5% vs. 4.5%, 4.5% vs. 2.8%, 4.5% vs. 1.1% and 1.1% vs. 3.9% of subjects).

Integration of data from Study 303, during which similar proportions of subjects experienced TEAEs and related TEAEs on OPC 50 mg and placebo, did not change the overall trend. There was no difference in the incidence of TESAEs assessed as related to OPC (25 mg and 50 mg) between the integrated population of Study 301 and Study 302 and the integrated population of all Phase III studies.

From the integrated database analysis of the DB period of the completed Phase III studies, including Study 303, the incidence of adverse drug reactions (ADRs) remains similar to the initial analysis, except for ADRs 'Fall' and 'Fatigue'. The MAH's proposal to include 'fall', 'fatigue' as uncommon ADRs in the SmPC is endorsed. Retained frequency of ADRs 'vomiting', 'muscle spasms' and 'hallucination visual' in the SmPC is also supported.

The MAH proposes to monitor and evaluate the post-authorisation safety profile of OPC in this extended indication as it has been doing for the originally approved indication, this is supported. In the Periodic Safety Update Report of *Ongentys* dystonia, diarrhoea and rhabdomyolysis are monitoring topics.

From the safety data presented, no new relevant safety findings of concern were identified, and the safety profile of OPC in subjects with PD without motor complications is generally consistent with the known safety profile in the current SmPC for *Ongentys*/*Ontilyv*. However, adding an additional agent on top of LD/DDCI increases safety issues. The adverse events, dyskinesia, nausea, vomiting, constipation, dry mouth and insomnia should be weighed against the marginal effect of opicapone in early Parkinson's Disease

5.5.1. Discussion on clinical safety

In the integrated population of all Phase 3 studies (DB periods of Study 301, Study 302 and Study 303), the most common TEAEs, reported at a higher incidence in subjects on OPC than on placebo, were dyskinesia, constipation, dry mouth and insomnia. In contrast, the most common TEAEs in Study 303, which enrolled subjects without motor fluctuations, were reported at a similar incidence (< 5.0 % difference) in the OPC 50 mg and placebo groups and included COVID-19, on and off phenomenon, back pain and tremor. No new safety signals were reported. The incidence, nature and severity of TEAEs, related TEAEs and serious TEAEs were similar between treatment groups. Moreover, the incidence and nature of TEAEs of special interest did not differ between the treatment groups. No deaths or serious AEs were reported due to OPC 50 mg treatment and the discontinuations due to TEAEs were similar in the OPC 50 mg group than in the placebo group. No clinically relevant trends were observed in the OPC 50 mg group for clinical laboratory including haematology, serum chemistry, or urinalysis, either in vital signs, physical and neurological examination, ECGs, C-SSRS, and mMIDI. Most of the AE are not life threatening, but the well-known increased frequency of troublesome gastrointestinal adverse events, sometimes with reduced quality of life, should be discussed.

5.5.2. Conclusions on clinical safety

Although the early stage of disease is different from the currently approved OPC indication, it can be considered that early stage PD patients are in principle the same population for which it is even expected that OPC would be better tolerated. Since the patients with PD disease studied in the pivotal Phase 3 study 303 for this extended indication have an earlier stage of the disease (without motor

fluctuations), the persistence of efficacy and tolerability is expected to be not substantially different from that in patients with end-of-dose motor fluctuations.

In the advanced stage of the actual indication, the majority of the adverse events were dopaminergic while it is expected that early PD patients may have a more preserved neuroplasticity and as such are able to better tolerate the intensified dopaminergic effect of OPC.

With regard to results from study 303 the OPC 50 mg once-daily oral dose was safe and well tolerated with no new safety signal reported for the use of OPC in PD patients without motor fluctuations. However, the adverse events, dyskinesia, nausea, vomiting, constipation, dry mouth and insomnia should be weighed against the marginal effect of opicapone in early Parkinson's Disease (see MO).

5.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

6. Risk management plan

The WSA submitted an updated RMP (version 6.1) with this application. The rationale for submitting an updated RMP is to include the new brand name (Ontilyv®) and the proposed indication. These minor changes affect the following part of the RMP:

Part I: Inclusion of the new brand name and the proposed indication.

Part II Module SI: Inclusion of the new brand name.

Part II module SIV: Inclusion of the new brand name.

Part VI: Inclusion of the new brand name.

The remaining parts of the RMP are not updated.

Rapporteur's comment

Since there were no additional pharmacovigilance activities or additional risk minimisation measures to address any safety concern, all safety concerns were deleted in the last version of the RMP approved (version 5) with the renewal procedure. With the safety data from this application, the Rapporteur does not consider necessary further updates of the RMP.

6.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable provides that the issues raised by the CHMP are solved.

7. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Please refer to separate Attachment which includes all proposed changes to the Product Information.

CHMP Comment

Currently, it is premature to comment on the PI because there is a MO objection which precludes approval of the extended indication.

7.1.1. User consultation

The Applicant submitted the following justification for waiving a readability testing:

Articles 59(3) and 61(1) of Directive 2001/83, as amended, require that package information leaflets (PIL) shall reflect the results of consultations with target patient groups to ensure that they are legible, clear and easy to use and the results of assessments carried out in co-operation with target patient groups shall also be provided to the competent authority. User testing was therefore performed and accepted by CHMP on the package leaflet for Ongentys, as part of the initial marketing authorisation application (MAA) concerning the approved indication: "Ongentys is indicated as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end of dose motor fluctuations who cannot be stabilised on those combinations".

The PIL for Ongentys 50 mg hard capsules was successfully readability tested in 2015 (parent PIL) (report reference BIA/053/01) and Ongentys 25 mg hard capsules (daughter PIL) was successfully bridged in parallel in 2015 (report reference BIA/053-BR-01). The MAH is now updating the clinical indication for Ongentys as a major type II variation. This waiver is submitted as part of the type II variation and intends to detail why no further readability studies are required for both strengths of the Ongentys leaflet.

OPC is also authorised by the European Commission since 21 February 2022 under the tradename Ontilyv relating to informed consent from Ongentys. The PIL for Ontilyv was successfully bridged (User testing bridging form) with PIL for Ongentys 50 mg hard capsules (parent PIL).

The content of the proposed updated Ongentys/Ontilyv Word PILs (50 mg and 25 mg hard capsules) are very similar to the parent and original daughter PILs, which have been successfully tested and bridged, respectively.

The Ongentys PIL is now being updated due to the addition of the new indication *for the treatment of signs and symptoms of* PD, the subject of this type II variation. The addition of the new indication for early stage PD targets a similar patient demographic group as made up the representative test population for the user testing previously performed. The proposed text modifications to the PL resulting from the addition of this new indication are minor and do not include text that is significantly different from that already user tested.

Overall, the layout, structure and design of the revised Ongentys Package Leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability. Therefore, the MAH does not consider it necessary to conduct further consultation with target patient groups further to that performed for the initial MAA.

CHMP comment:

As the structure of the PIL is not significantly altered by the introduced changes and the population who performed the user testing prior to introduction of the changes is similar to the new target population, it is agreed not to perform a new readability testing.

7.1.2. Additional monitoring

N/A

7.1.3. Quick Response (QR) code

N/A

8. Benefit-Risk Balance

8.1. Therapeutic Context

8.1.1. Disease or condition

Parkinson's disease is a neurological disorder with loss of dopamine generating neurons in the substantia nigra region of the mid brain and significant decrease in brain dopamine levels which result in typical Parkinson's symptoms. It is a degenerative disease that begins later in life: it is rare before 50 years of age, with a mean age of onset of about 60 years. The overall prevalence of Parkinson's disease for subjects aged 65 years or older is 1.6%. Prevalence increases with age, from 0.6% in the 65 to 69 years age group up to 3.5% in the 85 to 89 years age group.

The main features of Parkinson's disease are bradykinesia, tremor and rigidity, disturbances of movement, and problems with posture. Bradykinesia is the most disabling motor manifestation of Parkinson's disease, characterized by difficulty in initiating, and slowness in executing movements. The tremor occurs in the limbs while at rest and disappears on movement and during sleep. Rigidity refers to a resistance to passive movement and is often of a jerky or cogwheel nature. Other common symptoms of the disease are autonomic disturbances (sialorrhoea, seborrhoea, constipation, micturition disturbances, sexual functioning, orthostatic hypotension, hyperhidrosis), sleep disturbances, and disturbances in the sense of smell or sense of temperature. Depression and cognitive dysfunction is also common in Parkinson's disease patients.

8.1.2. Available therapies and unmet medical need

L-DOPA is the most effective symptomatic treatment of Parkinson's disease. Progression of the disease requires gradual increases in L-DOPA dosage to achieve adequate motor control, which in turn leads to development of motor complications such as motor fluctuations and dyskinesias. Orally administered L-DOPA is predominantly metabolised in the periphery by aromatic L-amino acid decarboxylase, also called dopa decarboxylase, to dopamine, which can cause side effects such as emesis, orthostatic hypotension, and cardiac arrhythmia. To minimise the formation of dopamine in the periphery, L-DOPA is usually administered in combination with a peripheral DDCI (benserazide or carbidopa). However, when administered together with such inhibitors, only a relatively small amount of an oral dose of L-DOPA reaches the brain because COMT becomes the major metabolising enzyme for L-DOPA, and a considerable amount of the drug undergoes O-methylation to 3-O-methyl-levodopa (3-OMD) in the brain and periphery.

COMT inhibitors are used as part of the treatment regimen to inhibit the O-methylation of L-DOPA to 3-OMD. COMT inhibition slows elimination of L-DOPA from the plasma by increasing its plasma half-life ($t_{1/2}$) and area under the curve (AUC) of plasma concentrations vs. time. The COMT inhibitors marketed to date are Tolcapone, Entacapone, and Opicapone. They have demonstrated beneficial effects both in experimental models of Parkinsonism and in Parkinson's disease patients.

Tolcapone is a more potent inhibitor of COMT than Entacapone, both in the periphery and central nervous system. However, due to an increased risk of hepatic toxicity with Tolcapone, its use is limited

to fluctuating patients who have failed other therapies or are intolerant to Entacapone. Entacapone, on the other hand, acts only in the periphery and is safer than Tolcapone although it is also contraindicated in patients with hepatic impairment, but has limited efficacy as well as low to moderate oral bioavailability which requires frequent dosing.

In general, there remains a lack of therapy alternatives for treatment of patients with earlier stages of Parkinson's disease (without motor fluctuations). Indeed, none of the approved COMT inhibitors are currently indicated for early-stage PD. There is probably a class effect of COMT inhibitors and since there is an unmet need and COMT inhibitors have been approved many years there have been off label prescription, several studies are performed and there are a lot of publications. There are two reasons to consider COMT inhibition in early stable disease, before the development of wearing-off. The first is to prevent prematurely the development of motor fluctuations, and the second is to alleviate the current symptoms in a stable patient who still benefits from levodopa therapy without diagnosed motor complications. Notably, it should be mentioned that a proportion of patients develop motor complications rather early within the first few years on the course of their disease[4][5].

8.1.3. Main clinical studies

The development program of OPC till date included 32 Phase I, 2 Phase II, 2 Phase III studies and 1 completed Phase IV study which provided data to support the use of OPC as adjunctive therapy to combinations of L-DOPA/DDCI in patients with Parkinson's disease who have motor fluctuations. The results of the Phase 2 and Phase 3 clinical efficacy studies are included in the initial MAA authorisation application. Study 303 is a Phase 3 double-blind, randomised, placebo-controlled and parallel-group study to evaluate the efficacy and safety of OPC as add-on to stable L-DOPA plus DDCI therapy in early idiopathic PD.

Overall, in clinical studies conducted so far, and including this latest 303 study in early PD, OPC has been administered at any dose to a total of 3003 subjects: 1277 healthy subjects, 2397 subjects with PD and motor fluctuations and 177 subjects with PD without motor fluctuations (see section 5.4.2, **Table** 1). In addition, at the cut-off date of 30th April 2023, a further 307 subjects had been exposed to OPC in the open-label (OL) part of the pivotal Phase 3 study 303 supporting the extension of indication. All doses of OPC were given orally in the clinical studies.

8.2. Favourable effects

The primary efficacy endpoint in study 303 was the change from baseline to the end of the DB period in MDS-UPDRS Part III total score. Secondary efficacy endpoints, considered exploratory, included the changes from baseline to post-baseline visits in the DB period in: MDS-UPDRS total scores for Parts I, II, III, and IV, and Parts II + III; modified Hoehn & Yahr staging total score; Schwab and England scale score; PDSS-2 total score; NMSS total and subdomain scores; PDQ-39 total and subdomain scores; the presence of individual symptoms, total and subsection (motor and non-motor) scores on the WOQ-9; and the proportion of subjects with improvement in CGI-I total score and PGI-I total score.

Analysis of the primary efficacy endpoint showed that the estimated mean change from baseline to the end of the 24-week DB period in MDS-UPDRS Part III total score was larger with OPC 50 mg (-6.5) than with placebo (-4.3) in the DB-FAS, with a mean treatment difference of -2.2 in favour of OPC

[4] Stocchi F, Jenner P, Obeso JA. When do levodopa motor fluctuations first appear in Parkinson's disease? Eur Neurol. 2010;63 (5):257–266.
[5] Stocchi F, Antonini A, Barone P, et al. Early Detection of wearing off in Parkinson disease: the DEEP study. Parkinsonism Relat Disord. 2014;20(2):204–211.

50 mg. However, the mean change from baseline in total score with placebo decreased through Week 4 and then started to rebound towards DB baseline. This divergence across time provided a near statistically significant difference at Week 12 (p=0.051) and a statistically significant difference at Week 24 (p=0.010) in favour of OPC 50 mg over placebo.

Results of the sensitivity analysis using control-based imputations and post-conflict data (Ukrainian study centres), and including results from the double-blind Per Protocol Analysis Set (DB-PPAS), were consistent with the primary analysis.

Analysis of all secondary endpoints was considered exploratory to identify any supportive clinical trend.

With regard to MDS-UPDRS Parts II + III total score, the estimated mean decrease from baseline at Week 24 was nominally statistically significantly greater with OPC 50 mg (-7.4) than with placebo (-4.6) (estimated mean difference of -2.8, p=0.036).

The mean scores for MDS UPDRS Part I and Part II showed only moderate improvement from baseline with OPC 50 mg and with placebo during the 24 weeks of treatment, with no statistically significant difference between treatment groups. Small but nominally statistically significant differences favouring opicapone were observed for nocturnal sleep disturbances (as assessed by the PDSS-2 total score), urinary symptoms (according to the NMSS, Domain 7) and PGI-I scores ((p=0.039, p<0.001, p=0.026, respectively).

According to the Investigators (CGI-I) and the subjects themselves (PGI-I), a greater proportion of subjects improved with OPC 50 mg (50.3% and 57.9%, respectively) compared to placebo (46.2% and 45.9%, respectively) at Week 24.

8.3. Uncertainties and limitations about favourable effects

In the study protocol it was defined that a minimum clinically relevant magnitude of effect in change from baseline of MDS-UPDRS Part III as primary endpoint between treatment arms (OPC versus Placebo) was expected to be at least 3-unit points, which has been definitely not achieved in the study. Hence, the MAH is asked to further discuss that moderate improvements of UPDRS score from baseline to the 6- month assessment correspond to clinically relevant changes. There remain uncertainties with respect to the clinical benefit in the intended target population.

Some clarification is needed in subpopulations e.g. females show a high placebo effect. Reasons for the rather small change of primary outcome parameter MDS-UPDRS Part III score compared to placebo need to be explored.

Effects on secondary endpoints are considered moderate. Most supportive secondary efficacy endpoints generally remained stable or showed only small not significant trends of improvement in favour of OPC 50 mg during the 24-week treatment period. The mean scores for MDS UPDRS Part I and Part II showed also only moderate improvement from baseline with OPC 50 mg and with placebo during the 24 weeks of treatment, with no statistically significant difference between treatment groups. The low values of these scores indicating low disease burden at baseline hamper the possibility to show a treatment effect.

Concerning the secondary endpoints, the clinical relevance of the observed treatment differences needs to be further evaluated.

Persistence of efficacy in subjects with Parkinson’s disease and end-of-dose motor fluctuations taking L-DOPA/DDCI has been demonstrated through the two OL extension periods of the Phase 3 studies conducted for the initial MAA (Study 301 and Study 302). Since the subjects with Parkinson’s disease studied in the pivotal Phase 3 study conducted for this extended indication (Study 303) have an earlier

stage of Parkinson's disease (without motor fluctuations), the persistence of efficacy and tolerability is expected to be not totally different from that in subjects with end-of-dose motor fluctuations. However, sustainability of clinical effects needs to be further justified and substantiated upon availability of the results of the 1-year open-label period of OPC 50 mg treatment. A short duration effect of OPC on outcome measures would be a critical limitation in early use of the disease.

8.4. Unfavourable effects

The safety profile of OPC in the extended indication population largely confirms the safety data from the previous initial application. The most prominent unfavourable effects are Nervous System Disorders and Infections and Infestations, reported at a similar incidence in the OPC 50 mg and placebo groups. The most commonly reported TEAEs (for > 3.0 % of subjects in any treatment group by PT) were reported at a similar incidence (< 5.0 % difference) in both treatment groups and included coronavirus disease 2019 (COVID-19), on and off phenomenon, back pain and tremor.

Integration of data from Study 303, during which similar proportions of subjects experienced TEAEs and related TEAEs on OPC 50 mg and placebo, did not change the overall trend. There was no difference in the incidence of TESAEs assessed as related to OPC (25 mg and 50 mg) between the integrated population of Study 301 and Study 302 and the integrated population of all Phase 3 studies.

From the integrated database analysis of the DB period of all completed Phase 3 studies, including Study 303, the majority of TEAEs were mild/moderate, with a low incidence of severe TEAEs regardless of the treatment group. The most common TEAEs with a higher incidence in subjects on OPC were dyskinesia, nausea, vomiting, constipation, dry mouth and insomnia. In contrast, the most common TEAEs in Study 303 were reported at a similar incidence in the OPC and placebo groups and included COVID-19, on and off phenomenon, back pain and tremor.

The long-term safety of OPC 50 mg was demonstrated in the OL periods of the Phase 3 studies of the initial MAA (Study 301 and Study 302) and is not expected to be any different in this population with earlier stage PD.

8.5. Uncertainties and limitations about unfavourable effects

All adverse drug reactions identified in the integrated safety analysis of the DP periods of all Phase 3 studies are considered expected as per approved SmPC except for two ADRs with frequency higher in the OPC than the Placebo group in the newly integrated safety analysis: 'Fall' and 'Fatigue' – the MAH proposes to include both ADRs in the revised product information with frequency 'uncommon'.

In early PD plasma levels can be controlled by dose adaptations of L-dopa by playing with dose and dose intervals. In late PD with motor fluctuation these options are limited. This has also been the argument for the indication PD with motor fluctuations and end-of-dose motor fluctuations. Moreover, adding an additional agent on top of LD/DDCI increases safety issues. Most of the AE are not life threatening, but the well-known increased frequency of troublesome gastrointestinal adverse events, sometimes with reduced quality of life, should be discussed. The natural course of PD is individual and especially in the early phase it can be difficult to distinguish a minor treatment effect from the natural course. To motivate the patients to put up with the side effects the effect must be unambiguous. The adverse events, dyskinesia, nausea, vomiting, constipation, dry mouth and insomnia should be weighed against the marginal effect of OPC in early PD.

8.6. Effects Table

Effect	Short description	Unit	Treatment OPC	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
MDS-UPDRS Part III Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	MDS-UPDRS Part III		N=176 -6.5 (0.69) (-7.9, -5.2)	N= 177 -4.3 (0.68) (-5.7, -3.0)	**SoE:** Difference between groups [LS Mean Diff. (SE)] -2.2 (0.86), p-value (MMRM) 0.010	study BIA-91067-303
MDS-UPDRS Part I Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	MDS-UPDRS Part I		0.4 (0.28) (-0.2, 1.0)	0.2 (0.28) (-0.4, 0.7)	**SoE:** Difference between groups [LS Mean Diff. (SE)] 0.2 (0.36), **Uncertainty:** p-value 0.512	study BIA-91067-303
MDS-UPDRS Part II Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	MDS-UPDRS Part I		-0.4 (0.34) (-1.1, 0.2)	0.3 (0.33) (-0.4, 0.9)	**SoE:** Difference between groups [LS Mean Diff. (SE)] -0.7 (0.44), **Uncertainty:** p-value 0.120	study BIA-91067-303
MDS-UPDRS Part IV Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	MDS-UPDRS Part IV		0.3 (0.08) (0.1, 0.4)	0.4 (0.08) (0.3, 0.6)	**SoE:** Difference between groups [LS Mean Diff. (SE)] -0.1 (0.11), **Uncertainty:** p-value 0.220	study BIA-91067-303
NMSS-total score and subdomain scores Least squares (LS) Mean (Standard error) (95% Confidence Interval for LS Mean)	NMSS-total score		-1.4 (0.96) (-3.3, 0.4)	0.5 (0.96) (-1.4, 2.4)	**SoE:** Difference between groups [LS Mean Diff. (SE)] -2.0 (1.21), **Uncertainty:** p-value 0.102	study BIA-91067-303
PDSS-2-total score Least squares (LS) Mean (Standard error) (95% Confidence	PDSS-2-total score		N=176 0.0 (0.57) (-1.2, 1.1)	N=177 1.4 (0.57) (0.3, 2.5)	**SoE:** Difference between groups [LS Mean Diff. (SE)] -1.5 (0.71), p-value 0.039	study BIA-91067-303

Effect	Short description	Unit	Treatment OPC	Control Placebo	Uncertainties / Strength of evidence	References
Interval for LS Mean)						
CGI-I total score The proportion of patients with any improvement at week 24	CGI-I total score	%	50.3	46.2	**SoE:** odds in favour of response 0.92 (OPC) and 0.78 (placebo) **Uncertainty:** p-value 0.493	study BIA-91067-303
PGI-I total score The proportion of patients with any improvement at week 24	PGI-I total score	%	57.9	45.9	**SoE:** odds in favour of response 1.18 (OPC) and 0.69 (placebo), p-value 0.026	study BIA-91067-303
Unfavourable Effects						
Study 303 (DB-SAF)						
On-off phenomena*		Number of subjects (%)	N=177 8 (4.5)	N=178 5 (2.8)	Higher incidence was reported in OPC compared to placebo, but with very low numbers.	Study 303 (DB-SAF)
Back pain*		Number of subjects (%)	N=177 8 (4.5)	N=178 2 (1.1)	Higher incidence was reported in OPC compared to placebo, but with very low numbers.	Study 303 (DB-SAF)
Tremor*		Number of subjects (%)	N=177 2 (1.1)	N=178 7 (3.9)	Higher incidence was reported in placebo compared to OPC, but with very low numbers.	Study 303 (DB-SAF)
Dyskinesia*		Number of subjects (%)	N=177 3 (1.7)	N=178 4 (2.2)	In the nervous system disorders similar incidences were reported in OPC and placebo	Study 303 (DB-SAF)
Nausea*		Number of subjects (%)	N=177 4 (2.3)	N=178 3 (1.7)	For nausea similar incidences were reported in OPC and placebo	Study 303 (DB-SAF)
Vomiting*		Number of subjects (%)	N=177 0 (0.0)	N=178 5 (2.8)	For vomiting however, clearly higher incidence was reported in placebo compared to OPC, but with very low numbers.	Study 303 (DB-SAF)
Insomnia*		Number of subjects (%)	N=177 4 (2.3)	N=178 1 (0.6)	Higher incidence was reported in OPC compared to placebo, but with very low numbers.	Study 303 (DB-SAF)
Integrated Studies 301, 302 and 303						
Dyskinesia**		Number of subjects (%)	N=686 96 (14.0)	N=435 20 (4.6)	Clearly higher incidence was reported in OPC compared to placebo.	Integrated Studies 301, 302 and 303
Dry mouth**		Number of subjects	N=686 26 (3.8)	N=435 3 (0.7)	Clearly higher incidence was reported in OPC	Integrated Studies 301, 302

Effect	Short description	Unit	Treatment OPC	Control Placebo	Uncertainties / Strength of evidence	References
		(%)			compared to placebo.	and 303
Constipation **		Number of subjects (%)	N=686 32 (4.7)	N=435 6 (1.4)	Clearly higher incidence was reported in OPC compared to placebo, but with low numbers.	Integrated Studies 301, 302 and 303
Nausea**		Number of subjects (%)	N=686 23 (3.4)	N=435 13 (3.0)	For nausea similar incidences were reported in OPC and placebo	Integrated Studies 301, 302 and 303
Vomiting**		Number of subjects (%)	N=686 8 (1.2)	N=435 10 (2.3)	For vomiting however, higher incidence was reported in placebo compared to OPC, but with low numbers.	Integrated Studies 301, 302 and 303
Back pain**		Number of subjects (%)	N=686 16 (2.3)	N=435 9 (2.1)	Similar incidences were reported in OPC and placebo	Integrated Studies 301, 302 and 303
Tremor**		Number of subjects (%)	N=686 12 (1.7)	N=435 11 (2.5)	Higher incidence was reported in placebo compared to OPC, but with very low numbers.	Integrated Studies 301, 302 and 303
Insomnia**		Number of subjects (%)	N=686 30 (4.4)	N=435 5 (1.1)	Clearly higher incidence was reported in OPC compared to placebo, but with low numbers.	Integrated Studies 301, 302 and 303

Abbreviations: CGI-I = Clinical Global Impression of Improvement, MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, NMSS = Non-motor Symptoms Scale, PDSS-2 = Parkinson's Disease Sleep Scale 2, PGI-I = Patient's Global Impression of Improvement

*Incidence of TEAEs reported for ≥2.0% of subjects in either treatment group by PT, by SOC and PT - Study 303 (DB-SAF),

** Integrated Studies 301, 302 and 303 OPC N=686, Placebo N=435

8.7. Benefit-risk assessment and discussion

8.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Findings from study 303 demonstrate that treatment with adjunct OPC 50 mg provides a statistically significant but clinically marginal effect in early, stably L-DOPA-treated patients. Analysis of the primary efficacy endpoint showed that the estimated mean change from baseline to the end of the 24-week DB period in MDS-UPDRS Part III total score was larger with OPC 50 mg (-6.5) than with placebo (-4.3) with a mean treatment difference of -2.2 in favour of OPC 50 mg. Also the placebo group shows a mean change from baseline in total score through Week 4 and then started to rebound towards DB baseline. This divergence across time provided a near statistically significant difference at Week 12

(p=0.051) and a statistically significant difference at Week 24 (p=0.010) in favour of OPC 50 mg over placebo.

Overall, the OPC 50 mg group met the primary efficacy objective of superiority against the placebo group based on the primary outcome parameter. However, the treatment difference between OPC and the placebo group is small and the clinical relevance is therefore questionable.

The analyses of the secondary endpoints were mostly moderate in favour to OPC 50 mg over placebo treatment, just the mean change from baseline to Week 24 for MDS-UPDRS Part II + III and the improvements reported by patients (PGI-I) were nominally statistically significantly better for OPC. OPC 50 mg was not associated with an increased development of motor complications when compared to placebo, as assessed by MDS-UPDRS Part IV. OPC 50 mg was also associated with a stabilization of the disease-related sleep disturbances, as assessed by the PDSS-2, in contrast with placebo.

Overall, the treatment effects were less pronounced and the results are not clearly convincing in favour of a clinical benefit of OPC 50 mg as adjunctive therapy to L-DOPA/DDCI in the extended indication of adult early stage PD patients without motor fluctuations.

Importance of unfavourable effects

Given the earlier stage of disease progression of the subjects in Study 303 compared with the currently approved OPC indication, it was expected that OPC would have an acceptable safety profile. In fact, in the DB period of Study 303, the overall incidence of TEAEs and related TEAEs was similar with OPC 50 mg compared to placebo, with few subjects experiencing TESAEs, severe TEAEs or TEAEs leading to treatment withdrawal. Nevertheless, integration of data from Study 303 with the DB period data from Study 301 and Study 302 (from the initial MAA) did not change the overall trend of higher incidence of TEAEs and related TEAEs with OPC than with placebo.

In the integrated population of all Phase 3 studies (DB periods of Study 301, Study 302 and Study 303), the most common TEAEs, reported at a higher incidence in subjects on OPC than on placebo, were dyskinesia, constipation, dry mouth and insomnia. In contrast, the most common TEAEs in Study 303, which enrolled subjects without motor fluctuations, were reported at a similar incidence (< 5.0 % difference) in the OPC 50 mg and placebo groups and included COVID-19, on and off phenomenon, back pain and tremor.

Parkinson's disease-related events (such as motor fluctuations and dyskinesias) were flagged as TEAEs of special interest in Study 303. These were reported at a similar incidence in subjects on OPC 50 mg (7.3%) and on placebo (6.7%), indicating no apparent increase in disease-related events with OPC 50 mg compared to placebo. The most common TEAE of special interest was on and off phenomenon (4.5 % vs. 2.8 %), followed by dyskinesia (1.7 % vs. 2.2 %). This is in contrast to the population with end-of-dose motor fluctuations (in Study 301 and Study 302) for which L-DOPA-related adverse reactions (dyskinesias, orthostatic hypotension, psychosis and psychotic disorders and impulse control disorders) showed a higher incidence in subjects taking OPC (as presented in initial MAA).

In line with the initial MAA, there was no apparent increase in the risk of hepatic or cardiac disorders with OPC 50 mg in the population of Study 303. Furthermore, there was no indication that OPC has any clinically significant effects on vital signs, physical and neurological examinations and ECG outcomes.

8.7.2. Balance of benefits and risks

The efficacy results get from study 303 generally do not clearly confirm that the overall benefit risk of OPC 50 mg in the extended indication as adjunctive therapy to L-DOPA/DDCI in adult patients for the

treatment of signs and symptoms of PD is considered favourable. The clinical relevance for the use of OPC in PD patients without motor fluctuations appears to be questionable and the well-known safety profile needs to be weighed against the marginal effect of opicapone in early PD.

8.7.3. Additional considerations on the benefit-risk balance

None

8.8. Conclusions

The indication is currently not approvable since a major objection is raised due a negative benefit/risk in light of the modest treatment effects and the small difference between the OPC and placebo group which need to be further justified. It is not clear if moderate improvements of UPDRS score from baseline to the 6- month assessment despite being statistically significant correspond to clinically relevant changes in early stage PD patients.

There are some other outstanding issues to be considered.